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(54) **COMPOSITIONS AND METHODS FOR TREATING ROTATOR CUFF INJURIES**

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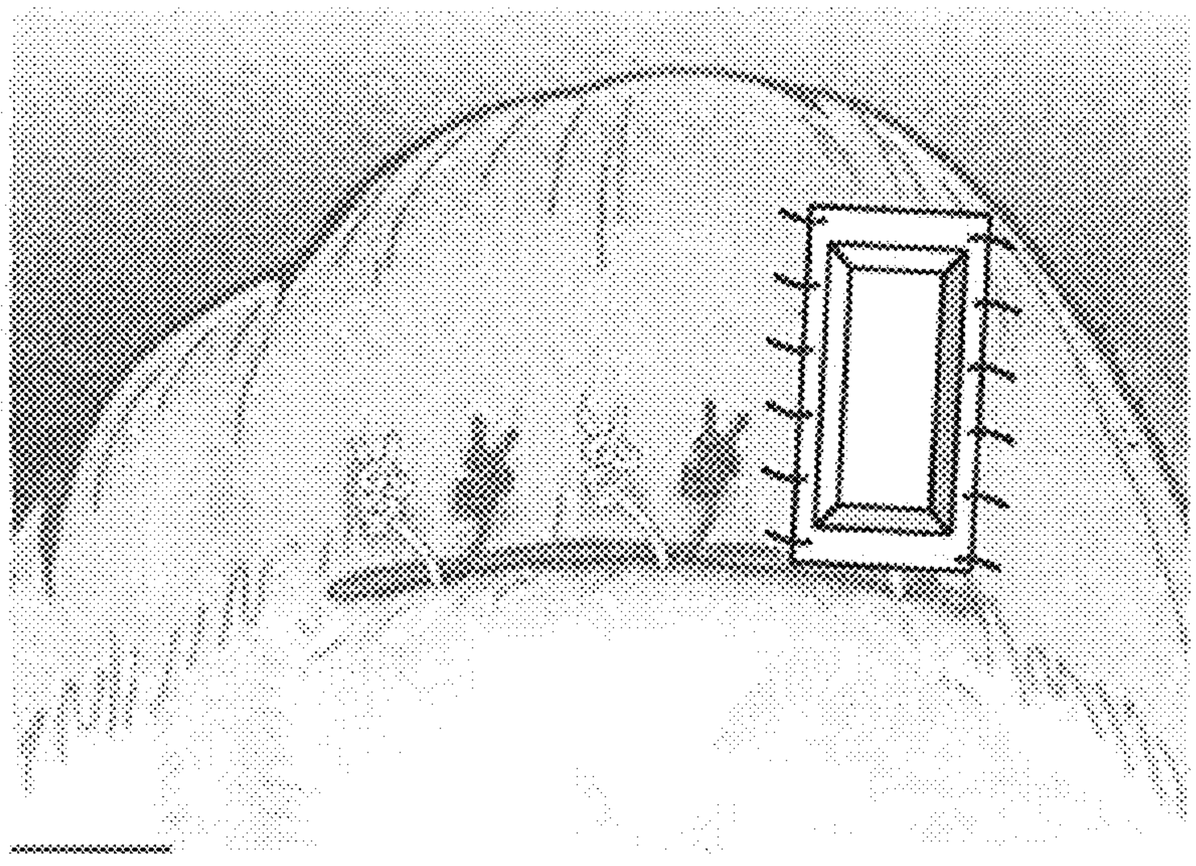
(57) **ABSTRACT**

The present invention provides compositions and methods for attaching tendon to bone. The present invention provides compositions and methods for treating rotator cuff injuries. In one embodiment, a method for treating rotator cuff injuries comprises providing a composition comprising PDGF disposed in a biocompatible matrix and applying the composition to at least one site of tendon reattachment on the humeral head.

27 Claims, 4 Drawing Sheets



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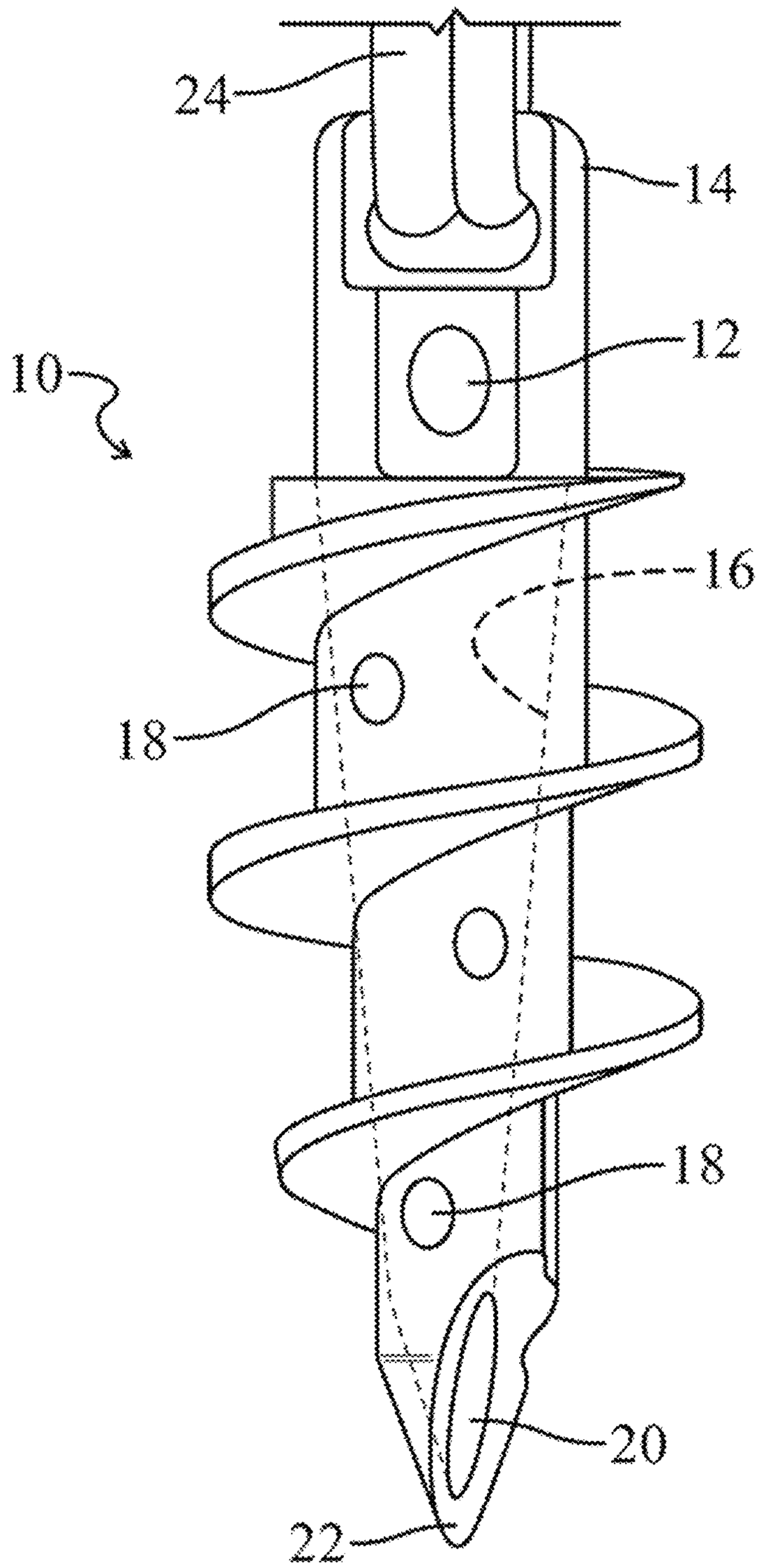
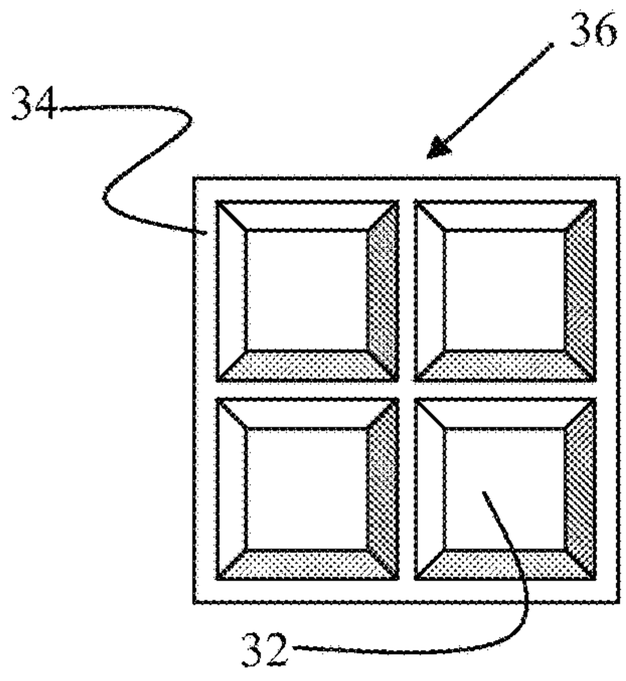


Fig. 1



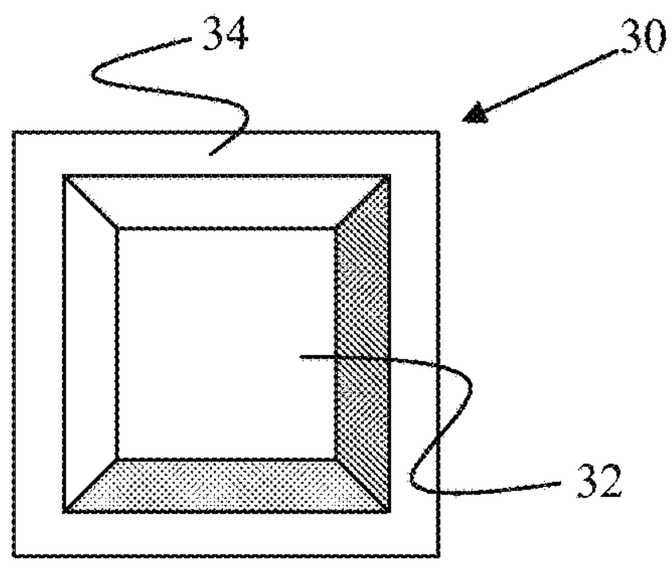


FIGURE 2

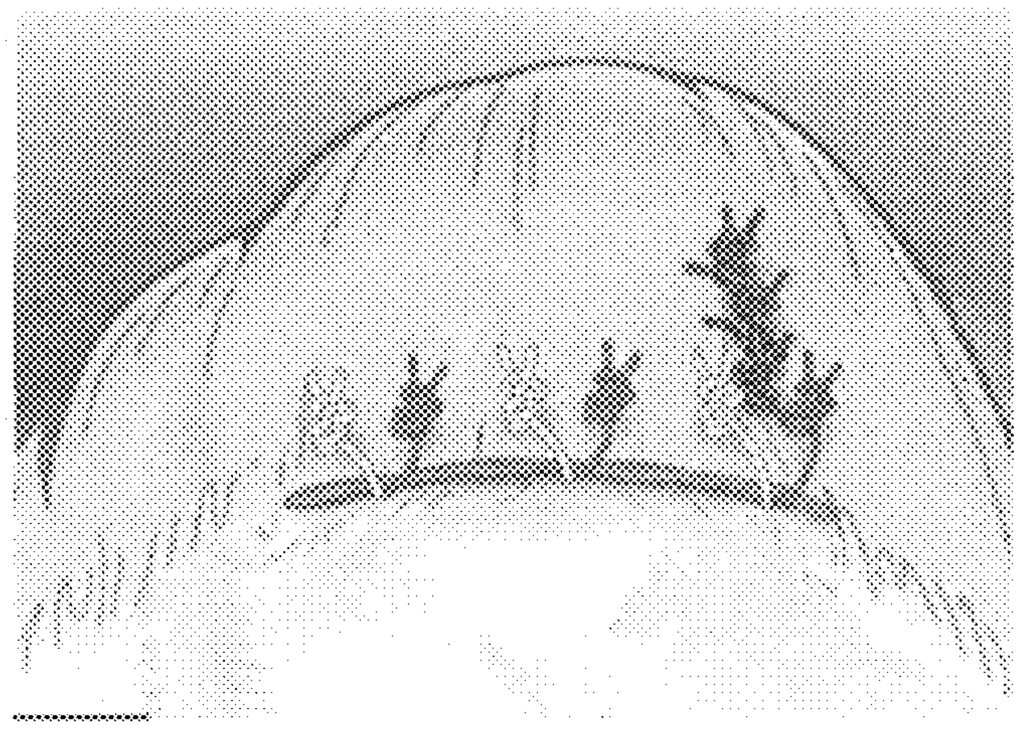


Fig. 3A

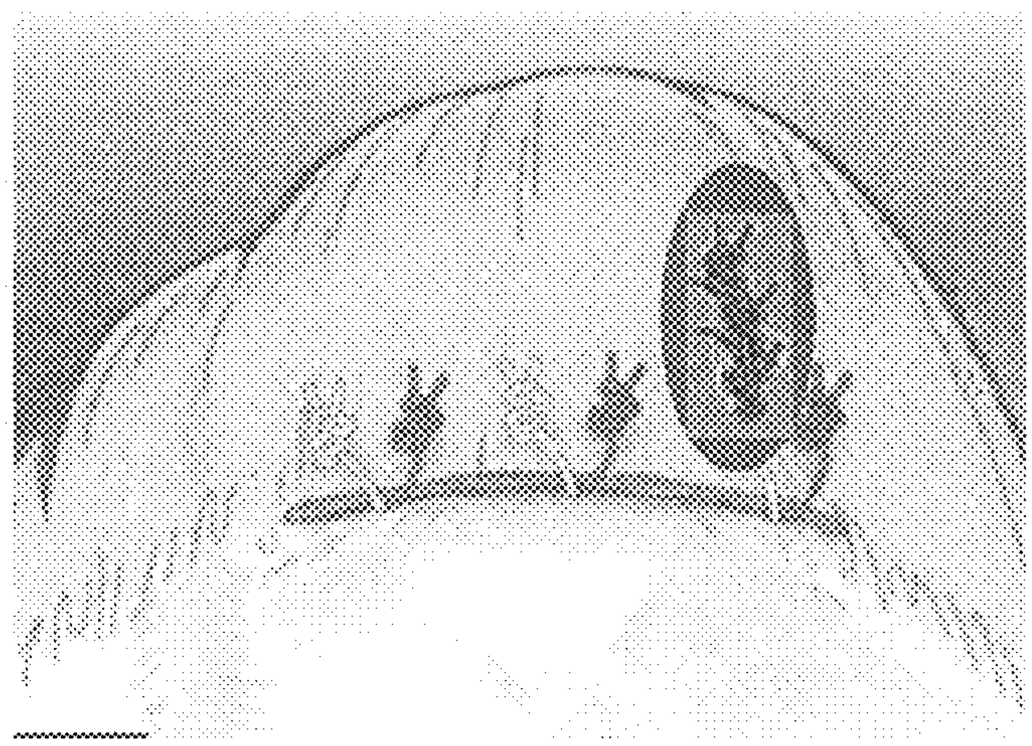


Fig. 3B

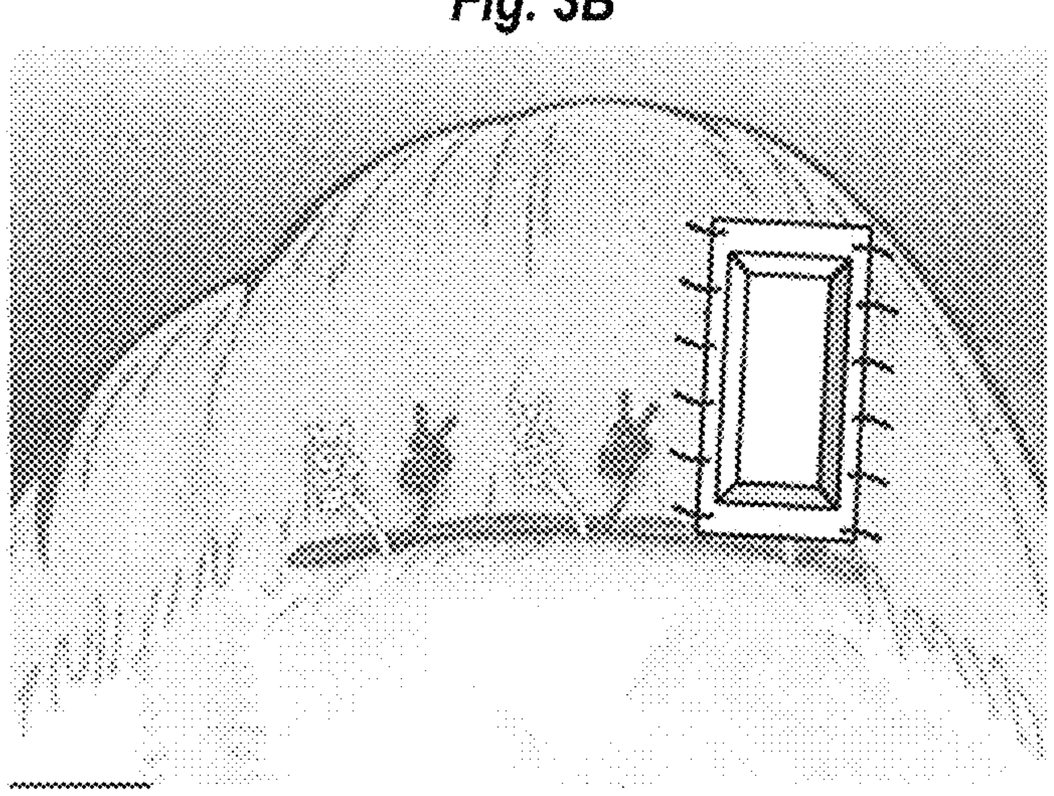


Fig. 3C

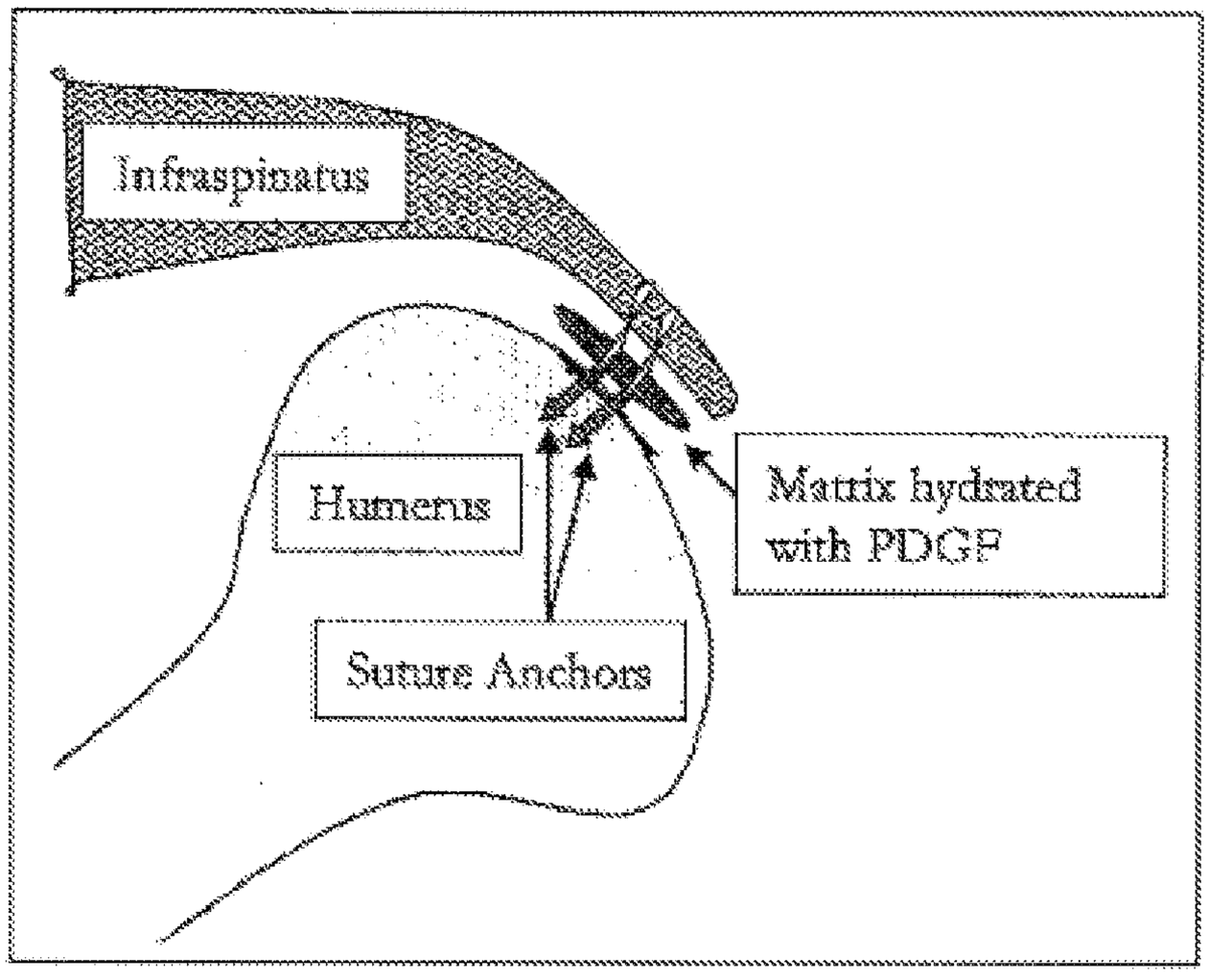

Infraspinatus
Humerus
Suture Anchors
Matrix hydrated with PDGF

FIGURE 4

COMPOSITIONS AND METHODS FOR TREATING ROTATOR CUFF INJURIES

RELATED APPLICATION DATA

This application is a continuation of U.S. application Ser. No. 15/476,394 filed on Mar. 31, 2017, which is a continuation of U.S. patent application Ser. No. 11/772,646 filed on Jul. 2, 2007, issued as U.S. Pat. No. 9,642,891 on May 9, 2017, which claims priority under 35 U.S.C. § 119 (e) to U.S. Provisional Patent Application Ser. No. 60/817,874 filed Jun. 30, 2006.

FIELD OF THE INVENTION

The present invention relates to compositions and methods useful for attaching tendon to bone, particularly for repairing rotator cuff injury.

BACKGROUND OF THE INVENTION

Hundreds of thousands of people experience tendon ruptures and tendon detachments from bone annually. Rotator cuff tears are among the most common injuries observed by practitioners of sports medicine. Approximately 400,000 rotator cuff repair surgeries are performed in the United States annually.

The rotator cuff is a group of four tendons which converge and surround the front, back, and top of the head of the humerus shoulder joint. These tendons are connected individually to short muscles that originate from the scapula. The muscles are referred to as the "SITS" muscles-supraspinatus, infraspinatus, teres minor and subscapularis. The muscles function to provide rotation and elevate the arm and give stability to the shoulder joint. When the muscles contract, they pull on the rotator cuff tendons, causing the shoulder to rotate upward, inward, or outward. There is a bursal sac between the rotator cuff and acromion that allows the muscles to glide freely when moving.

Rotator cuff tendons are susceptible to tears, which are a common source of shoulder pain. The tendons generally tear off at their insertion (attachment) onto the humeral head. Injuries to the rotator cuff may be present as complete evulsions, or L- or U-type partial tears. Pain, loss of motion and weakness may occur when one of the rotator cuff tendons tears. When rotator cuff tendons are injured or damaged, the bursa often becomes inflamed and may be an additional source of pain.

Notwithstanding surgical instrumentation and advanced techniques, the incidence of re-injury following repair of the rotator cuff is high, with some estimates approaching 70%. The failure of rotator cuff repairs has been attributed to the poor healing and reattachment of the muscles that insert on the humeral head. The normal fibrotic and proliferative response among tendon fibroblasts and mesenchymal stem cells is diminished within the shoulder. This inadequate healing response therefore transfers the burden of tendon reattachment and integrity to the mechanical strength of the sutures. Over time, the sutures break down and tear away from bone and/or tendon, causing re-injury of the shoulder. The problem has been documented in numerous studies employing the use of animal models. Coleman and colleagues report in *The Journal of Bone and Joint Surgery* 85:2391-2402 (2003) that the repaired infraspinatus muscle of the shoulder is capable of producing only 63% of the normal contraction force normal at 12 weeks after repair using a sheep model of chronic injury.

In view of the problems associated with rotator cuff repairs, it would be desirable to provide compositions and methods operable to improve the healing response associated with rotator cuff repairs. In particular, it would be desirable to provide compositions and methods which enhance fibrotic and proliferative responses among tendon fibroblasts and mesenchymal stems cells thereby promoting healing of a torn rotator cuff and tendon reattachment to the humeral head.

SUMMARY

The present invention provides compositions and methods for the treatment and/or repair of damaged tendons. In some embodiments, compositions and methods of the present invention are useful in the attachment or reattachment of tendons to bone, and may be applied to any tendon reattachment. In some embodiments, compositions and methods of the present invention enhance tendon attachment to bone by strengthening the tendon and/or bone at the site of tendon attachment to the bone. Moreover, the treatment of tendons encompasses application of compositions of the present invention to tendons, including damaged or injured tendons, such as tendons exhibiting tearing, delamination, and/or any other strain or deformation. Tendons which may be reattached to bone and/or treated by compositions and methods of the present invention include, but are not limited to, tendons of the subscapularis, supraspinatus, infraspinatus, teres minor, rectus femoris, tibialis posterior, and quadraceps femoris, as well as the Achilles Tendon, patellar tendon, abductor and adductor tendons, or other tendons of the hip.

In accordance with some embodiments of the present invention, there are provided compositions and methods for the treatment of rotator cuff tears. The present compositions and methods facilitate the healing response to rotator cuff repairs and tendon reattachment to the humeral head.

In one aspect, a composition provided by the present invention for promoting tendon reattachment to the humeral head comprises a solution comprising platelet derived growth factor (PDGF) and a biocompatible matrix, wherein the solution is disposed in the biocompatible matrix. In some embodiments, PDGF is present in the solution in a concentration ranging from about 0.01 mg/ml to about 10 mg/ml, from about 0.05 mg/ml to about 5 mg/ml, or from about 0.1 mg/ml to about 1.0 mg/ml. The concentration of PDGF within the solution may be within any of the concentration ranges stated above.

In embodiments of the present invention, PDGF comprises PDGF homodimers and heterodimers, including PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC, PDGF-DD, and mixtures and derivatives thereof. In one embodiment, PDGF comprises PDGF-BB. In another embodiment PDGF comprises a recombinant human (rh) PDGF such as recombinant human PDGF-BB (rhPDGF-BB).

In embodiments of the present invention, PDGF comprises PDGF fragments. In one embodiment rhPDGF-B comprises the following fragments: amino acid sequences 1-31, 1-32, 33-108, 33-109, and/or 1-108 of the entire B chain. The complete amino acid sequence (1-109) of the B chain of PDGF is provided in FIG. 15 of U.S. Pat. No. 5,516,896. It is to be understood that the rhPDGF compositions of the present invention may comprise a combination of intact rhPDGF-B (1-109) and fragments thereof. Other fragments of PDGF may be employed such as those disclosed in U.S. Pat. No. 5,516,896. In accordance with a preferred embodiment, the rhPDGF-BB comprises at least 65% of intact rhPDGF-B (1-109).

A biocompatible matrix, according to some embodiments of the present invention, comprises a bone scaffolding material. In some embodiments, a bone scaffolding material comprises calcium phosphate. Calcium phosphate, in one embodiment, comprises β-tricalcium phosphate (β-TCP)

In another aspect, the present invention provides a composition comprising a PDGF solution disposed in a biocompatible matrix, wherein the biocompatible matrix comprises a bone scaffolding material and a biocompatible binder. The PDGF solution may have a concentration of PDGF as described above. A bone scaffolding material, in some embodiments, comprises calcium phosphate. In one embodiment, a calcium phosphate comprises a β-TCP. In one aspect, biocompatible matrices may include calcium phosphate particles with or without biocompatible binders or bone allograft such as demineralized freeze dried bone allograft (DFDBA) or particulate demineralized bone matrix (DBM). In another aspect, biocompatible matrices may include bone allograft such as DFDBA or DBM.

Moreover, a biocompatible binder, according to some embodiments of the present invention, comprises proteins, polysaccharides, nucleic acids, carbohydrates, synthetic polymers, or mixtures thereof. In one embodiment, a biocompatible binder comprises collagen. In another embodiment, a biocompatible binder comprises collagen, such as bovine or human collagen.

The present invention additionally provides methods of producing compositions for the reattachment of tendons to bone, the strengthening of tendon attachment to bone, and/or the treatment of tendons including, but not limited to, those associated with rotator cuff tears. In one embodiment, a method for producing a composition comprises providing a solution comprising PDGF, providing a biocompatible matrix, and disposing the solution in the biocompatible matrix.

The present invention also provides methods for the reattachment of tendons to bone, the strengthening of tendon attachment to bone as well as methods for the treatment of tendons including damaged or injured tendons, such as those exhibiting tearing, delamination, or any other strain or deformation. In one embodiment, a method for attaching a tendon to bone and/or strengthening tendon attachment to bone comprises providing a composition comprising a PDGF solution disposed in a biocompatible matrix and applying the composition to at least one site of tendon reattachment on the bone. In another embodiment, a method for treating rotator cuff tears comprises providing a composition comprising a PDGF solution disposed in a biocompatible matrix and applying the composition to at least one site of tendon reattachment on the humeral head. In some embodiments, a method for treating a rotator cuff tear further comprises disposing at least one bone anchor in the humeral head, the at least one bone anchor further comprising a PDGF solution disposed in a biocompatible matrix, and coupling at least one detached tendon to the bone anchor.

In another embodiment, a method of treating a tendon comprises providing a composition comprising a PDGF solution disposed in a biocompatible matrix and applying the composition to a surface of at least one tendon. In some embodiments, the at least one tendon is an injured or damaged tendon, such as tendon exhibiting tearing, delamination, or any other deformation.

In some embodiments, the present invention may be used to repair a tendon tear that is not at a bone attachment point. Such a tendon tear may be sutured together with an overlay material which would release PDGF from the material. In some embodiments, for example, a tear occurs in midsubstance ruptures of the Achilles Tendon. Overlay materials for treating and/or repairing a tendon tear not at a point of bone attachment, in some embodiments, comprise biocompatible matrices including, but not limited to, fibrous collagen matrices, crosslinked hyaluron, allograft tissue, other synthetic matrices or combinations thereof.

In another aspect, the present invention provides a kit comprising a solution comprising PDGF in a first container and a second container comprising a biocompatible matrix. In some embodiments, the solution comprises a predetermined concentration of PDGF. The concentration of PDGF, in some embodiments, can be predetermined according to the nature of the tendon being treated. The kit may further comprise a scaffolding material and the scaffolding material may further comprise a biocompatible binder. Moreover, the amount of biocompatible matrix provided by a kit can be dependent on the nature of the tendon being treated. Biocompatible matrix that may be included in the kit may be a scaffolding material, a scaffolding material and a biocompatible binder, and/or bone allograft such as DFDBA or particulate DBM. In one embodiment the bone scaffolding material comprises a calcium phosphate, such as β-TCP. In another embodiment, a scaffolding material comprises a type I collagen patch as described herein. A syringe, in some embodiments, can facilitate disposition of the PDGF solution in the biocompatible matrix for application at a surgical site, such as a site of tendon attachment to bone. The kit may also contain instructions for use.

Accordingly it is an object of the present invention to provide a composition comprising PDGF useful in the attachment of tendon to bone.

Accordingly, it is an object of the present invention to provide a composition comprising PDGF useful for repair of tendons.

It is another object of the present invention to provide a method for attachment of tendon to bone using a composition comprising PDGF.

Another object of the present invention is to provide a composition comprising PDGF and method of using this composition to attach rotator cuff tendons to the humerus.

Another object of the present invention is to provide a composition comprising PDGF disposed in a matrix and further comprising a binder, and a method of using this composition to attach rotator cuff tendons to the humerus

These and other embodiments of the present invention are described in greater detail in the detailed description which follows. These and other objects, features and advantages of the present invention will become apparent after a review of the following detailed description of the disclosed embodiments and claims.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** illustrates a bone anchor according to an embodiment of the present invention.

FIG. **2** illustrates two embodiments, **30** and **36**, of an encapsulated PDGF composition, also showing a PDGF pouch **32** and a suturing border **34**.

FIGS. **3**A, **3**B and **3**C illustrate a prior art technique (**3**A), a PDGF containing pad incorporated into sutures (**3**B), and a PDGF pouch sutured over a repaired tear (**3**C).

FIG. **4** illustrates a surgical procedure according to one embodiment of the present invention.

DETAILED DESCRIPTION

The present invention provides compositions and methods for the treatment and/or repair of damaged tendons. In some embodiments, compositions and methods of the present invention are useful in the attachment or reattachment of tendons to bone, and may be applied to any tendon reattachment. In some embodiments, compositions and methods of the present invention enhance tendon attachment to bone by strengthening the tendon and/or bone at the site of tendon attachment to the bone. Moreover, the treatment of tendons encompasses application of compositions of the present invention to tendons, including damaged or injured tendons, such as tendons exhibiting tearing, delamination, and/or any other strain or deformation. Tendons which may be reattached to bone and/or treated by compositions and methods of the present invention include, but are not limited to, tendons of the subscapularis, supraspinatus, infraspinatus, teres minor, rectus femoris, tibialis posterior, and quadraceps femoris, as well as the Achilles Tendon, patellar tendon, abductor and adductor tendons, or other tendons of the hip.

The present invention, in one embodiment, for example, provides compositions and methods for the treatment of rotator cuff tears. As used herein, rotator cuff tears include complete tendon detachment as well as incomplete or partial tendon detachment. The present compositions and methods facilitate the healing response to rotator cuff repairs and tendon reattachment to the humeral head.

In one embodiment, a composition for promoting tendon reattachment to bone, such as the humeral head, comprises a solution comprising PDGF and a biocompatible matrix, wherein the solution is disposed in the biocompatible matrix. In another embodiment, a composition comprises a PDGF solution disposed in a biocompatible matrix, wherein the biocompatible matrix comprises a bone scaffolding material and a biocompatible binder. In one aspect, biocompatible matrices may include calcium phosphate particles with or without biocompatible binders or bone allograft such as DFDBA or particulate DBM. In another aspect, biocompatible matrices may include DFDBA or DBM.

Turning now to components that can be included in various embodiments of the present invention, compositions of the present invention comprise a solution comprising PDGF.

PDGF Solutions

In one aspect, a composition provided by the present invention comprises a solution comprising platelet derived growth factor (PDGF) and a biocompatible matrix, wherein the solution is disposed in the biocompatible matrix. In some embodiments, PDGF is present in the solution in a concentration ranging from about 0.01 mg/ml to about 10 mg/ml, from about 0.05 mg/ml to about 5 mg/ml, from about 0.1 mg/ml to about 1.0 mg/ml. PDGF may be present in the solution at any concentration within these stated ranges. In other embodiments, PDGF is present in the solution at any one of the following concentrations: about 0.05 mg/ml; about 0.1 mg/ml; about 0.15 mg/ml; about 0.2 mg/ml; about 0.25 mg/ml; about 0.3 mg/ml; about 0.35 mg/ml; about 0.4 mg/ml; about 0.45 mg/ml; about 0.5 mg/ml, about 0.55 mg/ml, about 0.6 mg/ml, about 0.65 mg/ml, about 0.7 mg/ml; about 0.75 mg/ml; about 0.8 mg/ml; about 0.85 mg/ml; about 0.9 mg/ml; about 0.95 mg/ml; or about 1.0 mg/ml. It is to be understood that these concentrations are simply examples of particular embodiments, and that the concentration of PDGF may be within any of the concentration ranges stated above.

Various amounts of PDGF may be used in the compositions of the present invention. Amounts of PDGF that could be used include amounts in the following ranges: about 1 μg to about 50 mg, about 10 μg to about 25 mg, about 100 μg to about 10 mg, and about 250 μg to about 5 mg.

The concentration of PDGF or other growth factors in embodiments of the present invention can be determined by using an enzyme-linked immunoassay as described in U.S. Pat. Nos. 6,221,625, 5,747,273, and 5,290,708, or any other assay known in the art for determining PDGF concentration. When provided herein, the molar concentration of PDGF is determined based on the molecular weight of PDGF dimer (e.g., PDGF-BB; MW about 25 kDa).

In embodiments of the present invention, PDGF comprises PDGF homodimers and heterodimers, including PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC, PDGF-DD, and mixtures and derivatives thereof. In one embodiment, PDGF comprises PDGF-BB. In another embodiment PDGF comprises a recombinant human PDGF, such as rhPDGF-BB.

PDGF, in some embodiments, can be obtained from natural sources. In other embodiments, PDGF can be produced by recombinant DNA techniques. In other embodiments, PDGF or fragments thereof may be produced using peptide synthesis techniques known to one of skill in the art, such as solid phase peptide synthesis. When obtained from natural sources, PDGF can be derived from biological fluids. Biological fluids, according to some embodiments, can comprise any treated or untreated fluid associated with living organisms including blood

Biological fluids, in another embodiment, can also comprise blood components including platelet concentrate (PC), apheresed platelets, platelet-rich plasma (PRP), plasma, serum, fresh frozen plasma (FFP), and buffy coat (BC). Biological fluids, in a further embodiment, can comprise platelets separated from plasma and resuspended in a physiological fluid.

When produced by recombinant DNA techniques, a DNA sequence encoding a single monomer (e.g., PDGF B-chain or A-chain), in some embodiments, can be inserted into cultured prokaryotic or eukaryotic cells for expression to subsequently produce the homodimer (e.g. PDGF-BB or PDGF-AA). In other embodiments, a PDGF heterodimer can be generated by inserting DNA sequences encoding for both monomeric units of the heterodimer into cultured prokaryotic or eukaryotic cells and allowing the translated monomeric units to be processed by the cells to produce the heterodimer (e.g. PDGF-AB). Commercially available cGMP recombinant PDGF-BB can be obtained commercially from Chiron Corporation (Emeryville, Calif.). Research grade rhPDGF-BB can be obtained from multiple sources including R&D Systems, Inc. (Minneapolis, Minn.), BD Biosciences (San Jose, Calif.), and Chemicon, International (Temecula, Calif.).

In embodiments of the present invention, PDGF comprises PDGF fragments. In one embodiment rhPDGF-B comprises the following fragments: amino acid sequences 1-31, 1-32, 33-108, 33-109, and/or 1-108 of the entire B chain. The complete amino acid sequence (1-109) of the B chain of PDGF is provided in FIG. 15 of U.S. Pat. No. 5,516,896. It is to be understood that the rhPDGF compositions of the present invention may comprise a combination of intact rhPDGF-B (1-109) and fragments thereof. Other fragments of PDGF may be employed such as those dis-

closed in U.S. Pat. No. 5,516,896. In accordance with one embodiment, the rhPDGF-BB comprises at least 65% of intact rhPDGF-B (1-109). In accordance with other embodiments, the rhPDGF-BB comprises at least 75%, 80%, 85%, 90%, 95%, or 99% of intact rhPDGF-B (1-109).

In some embodiments of the present invention, PDGF can be purified. Purified PDGF, as used herein, comprises compositions having greater than about 95% by weight PDGF prior to incorporation in solutions of the present invention. The solution may be any pharmaceutically acceptable solution. In other embodiments, the PDGF can be substantially purified. Substantially purified PDGF, as used herein, comprises compositions having about 5% to about 95% by weight PDGF prior to incorporation into solutions of the present invention. In one embodiment, substantially purified PDGF comprises compositions having about 65% to about 95% by weight PDGF prior to incorporation into solutions of the present invention. In other embodiments, substantially purified PDGF comprises compositions having about 70% to about 95%, about 75% to about 95%, about 80% to about 95%, about 85% to about 95%, or about 90% to about 95%, by weight PDGF, prior to incorporation into solutions of the present invention. Purified PDGF and substantially purified PDGF may be incorporated into scaffolds and binders.

In a further embodiment, PDGF can be partially purified. Partially purified PDGF, as used herein, comprises compositions having PDGF in the context of PRP, FFP, or any other blood product that requires collection and separation to produce PDGF. Embodiments of the present invention contemplate that any of the PDGF isoforms provided herein, including homodimers and heterodimers, can be purified or partially purified. Compositions of the present invention containing PDGF mixtures may contain PDGF isoforms or PDGF fragments in partially purified proportions. Partially purified and purified PDGF, in some embodiments, can be prepared as described in U.S. patent application Ser. No. 11/159,533 (Publication No: 20060084602).

In some embodiments, solutions comprising PDGF are formed by solubilizing PDGF in one or more buffers. Buffers suitable for use in PDGF solutions of the present invention can comprise, but are not limited to, carbonates, phosphates (e.g. phosphate buffered saline), histidine, acetates (e.g. sodium acetate), acidic buffers such as acetic acid and HCl, and organic buffers such as lysine, Tris buffers (e.g. tris(hydroxymethyl)aminoethane), N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES), and 3-(N-morpholino) propanesulfonic acid (MOPS). Buffers can be selected based on biocompatibility with PDGF and the buffer's ability to impede undesirable protein modification. Buffers can additionally be selected based on compatibility with host tissues. In one embodiment, sodium acetate buffer is used. The buffers may be employed at different molarities, for example about 0.1 mM to about 100 mM, about 1 mM to about 50 mM, about 5 mM to about 40 mM, about 10 mM to about 30 mM, or about 15 mM to about 25 mM, or any molarity within these ranges. In some embodiments, an acetate buffer is employed at a molarity of about 20 mM.

In another embodiment, solutions comprising PDGF are formed by solubilizing lyophilized PDGF in water, wherein prior to solubilization the PDGF is lyophilized from an appropriate buffer.

Solutions comprising PDGF, according to embodiments of the present invention, can have a pH ranging from about 3.0 to about 8.0. In one embodiment, a solution comprising PDGF has a pH ranging from about 5.0 to about 8.0, more preferably about 5.5 to about 7.0, most preferably about 5.5 to about 6.5, or any value within these ranges.

The pH of solutions comprising PDGF, in some embodiments, can be compatible with the prolonged stability and efficacy of PDGF or any other desired biologically active agent. PDGF is generally more stable in an acidic environment. Therefore, in accordance with one embodiment the present invention comprises an acidic storage formulation of a PDGF solution. In accordance with this embodiment, the PDGF solution preferably has a pH from about 3.0 to about 7.0, and more preferably from about 4.0 to about 6.5. The biological activity of PDGF, however, can be optimized in a solution having a neutral pH range. Therefore, in a further embodiment, the present invention comprises a neutral pH formulation of a PDGF solution. In accordance with this embodiment, the PDGF solution preferably has a pH from about 5.0 to about 8.0, more preferably about 5.5 to about 7.0, most preferably about 5.5 to about 6.5. In accordance with a method of the present invention, an acidic PDGF solution is reformulated to a neutral pH composition, wherein such composition is then used to treat bone, ligaments, tendons or cartilage in order to promote their growth and/or healing. In accordance with a preferred embodiment of the present invention, the PDGF utilized in the solutions is rhPDGF-BB.

In some embodiments, the pH of the PDGF containing solution may be altered to optimize the binding kinetics of PDGF to a matrix substrate or linker. If desired, as the pH of the material equilibrates to adjacent material, the bound PDGF may become labile.

The pH of solutions comprising PDGF, in some embodiments, can be controlled by the buffers recited herein. Various proteins demonstrate different pH ranges in which they are stable. Protein stabilities are primarily reflected by isoelectric points and charges on the proteins. The pH range can affect the conformational structure of a protein and the susceptibility of a protein to proteolytic degradation, hydrolysis, oxidation, and other processes that can result in modification to the structure and/or biological activity of the protein.

In some embodiments, solutions comprising PDGF can further comprise additional components, such as other biologically active agents. In other embodiments, solutions comprising PDGF can further comprise cell culture media, other stabilizing proteins such as albumin, antibacterial agents, protease inhibitors [e.g., ethylenediaminetetraacetic acid (EDTA), ethylene glycol-bis(beta-aminoethylether)-N,N',N'-tetraacetic acid (EGTA), aprotinin, ε-aminocaproic acid (EACA), etc.] and/or other growth factors such as fibroblast growth factors (FGFs), epidermal growth factors (EGFs), transforming growth factors (TGFs), keratinocyte growth factors (KGFs), insulin-like growth factors (IGFs), bone morphogenetic proteins (BMPs), or other PDGFs including compositions of PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC and/or PDGF-DD.

In addition to solutions comprising PDGF, compositions of the present invention also comprise a biocompatible matrix in which to dispose the PDGF solutions and may also comprise a biocompatible binder either with or without a biocompatible matrix.

Biocompatible Matrix

Scaffolding Material

A biocompatible matrix, according to embodiments of the present invention, comprises a scaffolding material. The scaffolding material, according to embodiments of the present invention, provides a framework or scaffold for new tissue growth to occur, including tendon and/or bone tissue. A scaffolding material, in some embodiments, comprises at least one calcium phosphate. In other embodiments, a scaf-

folding material can comprise a plurality of calcium phosphates. Calcium phosphates suitable for use as a scaffolding material, in embodiments of the present invention, have a calcium to phosphorus atomic ratio ranging from 0.5 to 2.0. In some embodiments the biocompatible matrix comprises an allograft such as DFDBA or particulate DBM.

Non-limiting examples of calcium phosphates suitable for use as bone scaffolding materials comprise amorphous calcium phosphate, monocalcium phosphate monohydrate (MCPM), monocalcium phosphate anhydrous (MCPA), dicalcium phosphate dihydrate (DCPD), dicalcium phosphate anhydrous (DCPA), octacalcium phosphate (OCP), a-tricalcium phosphate, β-TCP, hydroxyapatite (OHAp), poorly crystalline hydroxyapatite, tetracalcium phosphate (TTCP), heptacalcium decaphosphate, calcium metaphosphate, calcium pyrophosphate dihydrate, carbonated calcium phosphate, and calcium pyrophosphate.

Moreover, in some embodiments, a scaffolding material comprises a collagen patch or pad. A collagen patch or pad, in one embodiment of the present invention, comprises a fibrous collagen such as soluble type I bovine collagen. Fibrous collagen suitable for use in collagen patches or pads demonstrate sufficient mechanical properties, including wet tensile strength, to withstand suturing and hold a suture without tearing. In one embodiment, a collagen patch or pad has a density ranging from about 0.75 g/cm^3 to about 1.5 g/cm^3. Additionally, a collagen patch or pad for use in some embodiments of the present invention is porous and operable to absorb water in an amount ranging from about 1× to about 15× the mass of the collagen patch.

In some embodiments, a scaffolding material comprises porous structure. Porous bone scaffolding materials, according to some embodiments, can comprise pores having diameters ranging from about 1 μm to about 1 mm. In one embodiment, a scaffolding material comprises macropores having diameters ranging from about 100 μm to about 1 mm. In another embodiment, a scaffolding material comprises mesopores having diameters ranging from about 10 μm to about 100 μm. In a further embodiment, a scaffolding material comprises micropores having diameters less than about 10 μm. Embodiments of the present invention contemplate scaffolding materials comprising macropores, mesopores, and micropores or any combination thereof.

A porous scaffolding material, in one embodiment, has a porosity greater than about 25%. In another embodiment, a porous scaffolding material has a porosity greater than about 50%. In a further embodiment, a porous scaffolding material has a porosity greater than about 90%.

In some embodiments, a scaffolding material comprises a plurality of particles. A scaffolding material, for example, can comprise a plurality of calcium phosphate particles. Scaffolding particles, in one embodiment, have an average diameter ranging from about 1 μm to about 5 mm. In other embodiments, particles have an average diameter ranging from about 250 μm to about 750 μm. Scaffolding particles, in another embodiment, can have average diameter ranging from about 100 μm to about 400 μm. In a further embodiment, the particles have an average diameter ranging from about 75 μm to about 300 μm. In additional embodiments, scaffolding particles have an average diameter less than about 1 μm and, in some cases, less than about 1 mm.

Scaffolding materials, according to some embodiments, can be provided in a shape suitable for implantation (e.g., a sphere, a cylinder, or a block). In other embodiments, bone scaffolding materials are moldable, extrudable, and/or injectable. Moldable scaffolding materials can facilitate efficient placement of compositions of the present invention in and around tendons and/or bone, including sites of tendon attachment to bone. In some embodiments, moldable scaffolding materials are applied to bone and/or tendons with a spatula or equivalent device. In some embodiments, scaffolding materials are flowable. Flowable scaffolding materials, in some embodiments, can be applied to tendon reattachment sites through a syringe and needle or cannula. In some embodiments, the flowable scaffolding materials can be applied to sites of tendon reattachment percutaneously. In other embodiments, flowable scaffolding materials can be applied to a surgically exposed site of tendon reattachment. In a further embodiment, moldable and/or flowable scaffolding materials can be applied to bone anchors used in the reattachment of a tendon to a bone.

In some embodiments, scaffolding materials are bioresorbable. A scaffolding material, in one embodiment, can be resorbed within one year of in vivo implantation. In another embodiment, a scaffolding material can be resorbed within 1, 3, 6, or 9 months of in vivo implantation. Bioresorbability is dependent on: (1) the nature of the matrix material (i.e., its chemical make up, physical structure and size); (2) the location within the body in which the matrix is placed; (3) the amount of matrix material that is used; (4) the metabolic state of the patient (diabetic/non-diabetic, osteoporotic, smoker, old age, steroid use, etc.); (5) the extent and/or type of injury treated; and (6) the use of other materials in addition to the matrix such as other bone anabolic, catabolic and anti-catabolic factors.

Scaffolding Comprising β-Tricalcium Phosphate (β-TCP)

A scaffolding material for use as a biocompatible matrix, in some embodiments, comprises β-TCP. β-TCP, according to some embodiments, can comprise a porous structure having multidirectional and interconnected pores of varying diameters. In some embodiments, β-TCP comprises a plurality of pockets and non-interconnected pores of various diameters in addition to the interconnected pores. The porous structure of β-TCP, in one embodiment, comprises macropores having diameters ranging from about 100 μm to about 1 mm, mesopores having diameters ranging from about 10 μm to about 100 μm, and micropores having diameters less than about 10 μm. Macropores and micropores of the β-TCP can facilitate tissue in-growth including osteoinduction and osteoconduction while macropores, mesopores and micropores can permit fluid communication and nutrient transport to support tissue and bone regrowth throughout the β-TCP biocompatible matrix.

In comprising a porous structure, β-TCP, in some embodiments, can have a porosity greater than 25%. In other embodiments, β-TCP can have a porosity greater than 50%. In a further embodiment, β-TCP can have a porosity greater than 90%.

In some embodiments, a bone scaffolding material comprises β-TCP particles. β-TCP particles, in one embodiment, have an average diameter ranging from about 1 μm to about 5 mm. In other embodiments, β-TCP particles have an average diameter ranging from about 250 μm to about 750 μm. In another embodiment, β-TCP particles have an average diameter ranging from about 100 μm to about 400 μm. In a further embodiment, β-TCP particles have an average diameter ranging from about 75 μm to about 300 μm. In additional embodiments, β-TCP particles have an average diameter less than 25 μm and, in some cases, sizes less than 1 mm.

A biocompatible matrix comprising a β-TCP scaffolding material, in some embodiments, is provided in a shape suitable for implantation (e.g., a sphere, a cylinder, or a block). In other embodiments, a β-TCP scaffolding material

is moldable, extrudable, and/or flowable thereby facilitating application of the matrix in areas of tendon reattachment, such as channels in the humeral head. Flowable matrices may be applied through syringes, tubes, or spatulas. In some embodiments, moldable, extrudable, and/or flowable β-TCP scaffolding materials are applied to bone anchors used in the reattachment of tendons to bone.

A β-TCP scaffolding material, according to some embodiments, is bioresorbable. In one embodiment, a β-TCP scaffolding material can be at least 75% resorbed one year subsequent to in vivo implantation. In another embodiment, a β-TCP bone scaffolding material can be greater than 90% resorbed one year subsequent to in vivo implantation.

Scaffolding Material Comprising a Collagen Patch

In some embodiments, a scaffolding material comprises a collagen patch or pad. A collagen patch or pad, in one embodiment of the present invention, comprises a fibrous collagen such as soluble type I bovine collagen. In another embodiment, a fibrous collagen comprises type II or type III collagen. Fibrous collagen suitable for use in collagen patches or pads demonstrate sufficient mechanical properties, including wet tensile strength, to withstand suturing and hold a suture without tearing. A fibrous collagen patch, for example, can have a wet tear strength ranging from about 0.75 pounds to about 5 pounds. In one embodiment, a collagen patch or pad has a density ranging from about 0.75 g/cm^3 to about 1.5 g/cm^3. Additionally, a collagen patch or pad for use in some embodiments of the present invention is porous and operable to absorb water in an amount ranging from about 1× to about 15× the mass of the collagen patch.

Scaffolding Material and Biocompatible Binder

In another embodiment, a biocompatible matrix comprises a scaffolding material and a biocompatible binder. Biocompatible matrices comprising a scaffolding material and a biocompatible binder, according to embodiments of the present invention, are useful for the repair, strengthening, and/or reattachment of tendons to bone by providing a structure for new tendon and/or bone tissue growth.

Biocompatible binders, according to some embodiments, can comprise materials operable to promote cohesion between combined substances. A biocompatible binder, for example, can promote adhesion between particles of a bone scaffolding material in the formation of a biocompatible matrix. In certain embodiments, the same material may serve as both a scaffolding material and a binder if such material acts to promote cohesion between the combined substances and provides a framework for new tissue growth to occur, including tendon and bone growth.

Biocompatible binders, in some embodiments, can comprise collagen, elastin, polysaccharides, nucleic acids, carbohydrates, proteins, polypeptides, poly(α-hydroxy acids), poly(lactones), poly(amino acids), poly(anhydrides), polyurethanes, poly(orthoesters), poly(anhydride-co-imides), poly(orthocarbonates), poly(α-hydroxy alkanoates), poly (dioxanones), poly(phosphoesters), polylactic acid, poly(L-lactide) (PLLA), poly(D,L-lactide) (PDLLA), polyglycolide (PGA), poly(lactide-co-glycolide (PLGA), poly(L-lactide-co-D, L-lactide), poly(D,L-lactide-co-trimethylene carbonate), polyglycolic acid, polyhydroxybutyrate (PHB), poly(ε-caprolactone), poly(δ-valerolactone), poly(γ-butyrolactone), poly(caprolactone), polyacrylic acid, polycarboxylic acid, poly(allylamine hydrochloride), poly(diallyldimethylammonium chloride), poly(ethyleneimine), polypropylene fumarate, polyvinyl alcohol, polyvinylpyrrolidone, polyethylene, polymethylmethacrylate, carbon fibers, poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidone), poly(ethyloxazoline), poly(ethylene oxide)-co-polypropylene oxide) block copolymers, poly (ethylene terephthalate)polyamide, and copolymers and mixtures thereof.

Biocompatible binders, in other embodiments, can comprise alginic acid, arabic gum, guar gum, xantham gum, gelatin, chitin, chitosan, chitosan acetate, chitosan lactate, chondroitin sulfate, N,O-carboxymethyl chitosan, a dextran (e.g., α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, or sodium dextran sulfate), fibrin glue, lecithin, phosphatidylcholine derivatives, glycerol, hyaluronic acid, sodium hyaluronate, a cellulose (e.g., methylcellulose, carboxymethylcellulose, hydroxypropyl methylcellulose, or hydroxyethyl cellulose), a glucosamine, a proteoglycan, a starch (e.g., hydroxyethyl starch or starch soluble), lactic acid, a pluronic acids, sodium glycerophosphate, glycogen, a keratin, silk, and derivatives and mixtures thereof.

In some embodiments, a biocompatible binder is water-soluble. A water-soluble binder can dissolve from the biocompatible matrix shortly after its implantation, thereby introducing macroporosity into the biocompatible matrix. Macroporosity, as discussed herein, can increase the osteoconductivity of the implant material by enhancing the access and, consequently, the remodeling activity of the osteoclasts and osteoblasts at the implant site.

In some embodiments, a biocompatible binder can be present in a biocompatible matrix in an amount ranging from about 5 weight percent to about 50 weight percent of the matrix. In other embodiments, a biocompatible binder can be present in an amount ranging from about 10 weight percent to about 40 weight percent of the biocompatible matrix. In another embodiment, a biocompatible binder can be present in an amount ranging from about 15 weight percent to about 35 weight percent of the biocompatible matrix. In a further embodiment, a biocompatible binder can be present in an amount of about 20 weight percent of the biocompatible matrix.

A biocompatible matrix comprising a scaffolding material and a biocompatible binder, according to some embodiments, can be flowable, moldable, and/or extrudable. In such embodiments, a biocompatible matrix can be in the form of a paste or putty. A biocompatible matrix in the form of a paste or putty, in one embodiment, can comprise particles of a scaffolding material adhered to one another by a biocompatible binder.

A biocompatible matrix in paste or putty form can be molded into the desired implant shape or can be molded to the contours of the implantation site. In one embodiment, a biocompatible matrix in paste or putty form can be injected into an implantation site with a syringe or cannula. In a further embodiment, moldable and/or flowable scaffolding materials can be applied to bone anchors used in the reattachment of a tendon to a bone.

In some embodiments, a biocompatible matrix in paste or putty form does not harden and retains a flowable and moldable form subsequent to implantation. In other embodiments, a paste or putty can harden subsequent to implantation, thereby reducing matrix flowability and moldability.

A biocompatible matrix comprising a scaffolding material and a biocompatible binder, in some embodiments, can also be provided in a predetermined shape including a block, sphere, or cylinder or any desired shape, for example a shape defined by a mold or a site of application.

A biocompatible matrix comprising a scaffolding material and a biocompatible binder, in some embodiments, is bioresorbable. A biocompatible matrix, in such embodiments, can be resorbed within one year of in vivo implantation. In another embodiment, a biocompatible matrix comprising a

bone scaffolding material and a biocompatible binder can be resorbed within 1, 3, 6, or 9 months of in vivo implantation. Bioresorbablity, in some embodiments, is dependent on: (1) the nature of the matrix material (i.e., its chemical make up, physical structure and size); (2) the location within the body in which the matrix is placed; (3) the amount of matrix material that is used; (4) the metabolic state of the patient (diabetic/non-diabetic, osteoporotic, smoker, old age, steroid use, etc.); (5) the extent and/or type of injury treated; and (6) the use of other materials in addition to the matrix such as other bone anabolic, catabolic and anti-catabolic factors.

Biocompatible Matrix Comprising β-TCP and Collagen

In some embodiments, a biocompatible matrix can comprise a β-TCP scaffolding material and a biocompatible collagen binder. β-TCP scaffolding materials suitable for combination with a collagen binder are consistent with those provided hereinabove.

A collagen binder, in some embodiments, comprises any type of collagen, including Type I, Type II, and Type III collagens. In one embodiment, a collagen binder comprises a mixture of collagens, such as a mixture of Type I and Type II collagen. In other embodiments, a collagen binder is soluble under physiological conditions. Other types of collagen present in bone or musculoskeletal tissues may be employed. Recombinant, synthetic and naturally occurring forms of collagen may be used in the present invention.

A biocompatible matrix, according to some embodiments, comprises a plurality of β-TCP particles adhered to one another with a collagen binder. In one embodiment, β-TCP particles suitable for combination with a collagen binder have an average diameter ranging from about 1 μm to about 5 mm. In another embodiment, β-TCP particles suitable for combination with a collagen binder have an average diameter ranging from about 1 μm to about 1 mm. In other embodiments, β-TCP particles have an average diameter ranging from about 200 μm to about 3 mm or about 200 μm to about 1 mm, or about 1 mm to about 2 mm. In some embodiments, β-TCP particles have an average diameter ranging from about 250 μm to about 750 μm. β-TCP particles, in other embodiments, have an average diameter ranging from about 100 μm to about 400 μm. In a further embodiment, β-TCP particles have an average diameter ranging from about 75 μm to about 300 μm. In additional embodiments, β-TCP particles have an average diameter less than about 25 μm and, in some cases, less than about 1 mm.

β-TCP particles, in some embodiments, can be adhered to one another by the collagen binder so as to produce a biocompatible matrix having a porous structure. In some embodiments, a biocompatible matrix comprising β-TCP particles and a collagen binder can comprise pores having diameters ranging from about 1 μm to about 1 mm. A biocompatible matrix comprising β-TCP particles and a collagen binder can comprise macropores having diameters ranging from about 100 μm to about 1 mm, mesopores having diameters ranging from about 10 μm to 100 μm, and micropores having diameters less than about 10 μm.

A biocompatible matrix comprising β-TCP particles and a collagen binder can have a porosity greater than about 25%. In another embodiment, the biocompatible matrix can have a porosity greater than about 50%. In a further embodiment, the biocompatible matrix can have a porosity greater than about 90%.

A biocompatible matrix comprising β-TCP particles, in some embodiments, can comprise a collagen binder in an amount ranging from about 5 weight percent to about 50 weight percent of the matrix. In other embodiments, a collagen binder can be present in an amount ranging from about 10 weight percent to about 40 weight percent of the biocompatible matrix. In another embodiment, a collagen binder can be present in an amount ranging from about 15 weight percent to about 35 weight percent of the biocompatible matrix. In a further embodiment, a collagen binder can be present in an amount of about 20 weight percent of the biocompatible matrix.

A biocompatible matrix comprising β-TCP particles and a collagen binder, according to some embodiments, can be flowable, moldable, and/or extrudable. In such embodiments, the biocompatible matrix can be in the form of a paste or putty. A paste or putty can be molded into the desired implant shape or can be molded to the contours of the implantation site. In one embodiment, a biocompatible matrix in paste or putty form comprising β-TCP particles and a collagen binder can be injected into an implantation site with a syringe or cannula. In a further embodiment, moldable, extrudable, and/or flowable matrix comprising β-TCP particles and a collagen binder can be applied to bone anchors and/or sutures used in the reattachment of a tendon to a bone.

In some embodiments, a biocompatible matrix in paste or putty form comprising β-TCP particles and a collagen binder can retain a flowable and moldable form when implanted. In other embodiments, the paste or putty can harden subsequent to implantation, thereby reducing matrix flowability and moldability.

A biocompatible matrix comprising β-TCP particles and a collagen binder, in some embodiments, can be provided in a predetermined shape such as a block, sphere, or cylinder.

A biocompatible matrix comprising β-TCP particles and a collagen binder can be resorbable. In one embodiment, a biocompatible matrix comprising β-TCP particles and a collagen binder can be at least 75% resorbed one year subsequent to in vivo implantation. In another embodiment, a biocompatible matrix comprising β-TCP particles and a collagen binder can be greater than 90% resorbed one year subsequent to in vivo implantation.

In some embodiments, a solution comprising PDGF can be disposed in a biocompatible matrix to produce a composition for the treatment of rotator cuff tears.

Disposing PDGF Solution in a Biocompatible Matrix

In another aspect, the present invention provides methods for producing compositions for use in the treatment of damaged or injured tendons, including those associated with torn rotator cuffs. In one embodiment, a method for producing such compositions for the treatment of tendons and/or bone comprises providing a solution comprising PDGF, providing a biocompatible matrix, and disposing the solution in the biocompatible matrix. PDGF solutions and biocompatible matrices suitable for combination are consistent with those described hereinabove.

In some embodiments, a PDGF solution can be disposed in a biocompatible matrix by soaking the biocompatible matrix in the PDGF solution. A PDGF solution, in another embodiment, can be disposed in a biocompatible matrix by injecting the biocompatible matrix with the PDGF solution. In some embodiments, injecting a PDGF solution can comprise disposing the PDGF solution in a syringe and expelling the PDGF solution into the biocompatible matrix to saturate the biocompatible matrix.

The biocompatible matrix, according to some embodiments, can be in a predetermined shape, such as a brick or cylinder, prior to receiving a PDGF solution. Subsequent to receiving a PDGF solution, the biocompatible matrix can

have a paste or putty form that is flowable, extrudable, and/or injectable. In other embodiments, the biocompatible matrix can already demonstrate a flowable paste or putty form prior to receiving a solution comprising PDGF.

Compositions Further Comprising Biologically Active Agents

Compositions of the present invention, according to some embodiments, further comprise one or more biologically active agents in addition to PDGF. Biologically active agents that can be incorporated into compositions of the present invention, in addition to PDGF, can comprise organic molecules, inorganic materials, proteins, peptides, nucleic acids (e.g., genes, gene fragments, small-insert ribonucleic acids [si-RNAs], gene regulatory sequences, nuclear transcriptional factors and antisense molecules), nucleoproteins, polysaccharides (e.g., heparin), glycoproteins, and lipoproteins. Non-limiting examples of biologically active compounds that can be incorporated into compositions of the present invention, including, e.g., anti-cancer agents, antibiotics, analgesics, anti-inflammatory agents, immunosuppressants, enzyme inhibitors, antihistamines, hormones, muscle relaxants, prostaglandins, trophic factors, osteoinductive proteins, growth factors, and vaccines, are disclosed in U.S. patent application Ser. No. 11/159,533 (Publication No: 20060084602). Biologically active compounds that can be incorporated into compositions of the present invention, in some embodiments, include osteoinductive factors such as insulin-like growth factors, fibroblast growth factors, or other PDGFs. In accordance with other embodiments, biologically active compounds that can be incorporated into compositions of the present invention preferably include osteoinductive and osteostimulatory factors such as bone morphogenetic proteins (BMPs), BMP mimetics, calcitonin, calcitonin mimetics, statins, statin derivatives, fibroblast growth factors, insulin-like growth factors, growth differentiating factors, and/or parathyroid hormone. Additional factors for incorporation into compositions of the present invention, in some embodiments, include protease inhibitors, as well as osteoporotic treatments that decrease bone resorption including bisphosphonates, and antibodies to the NF-kB (RANK) ligand.

Standard protocols and regimens for delivery of additional biologically active agents are known in the art. Additional biologically active agents can introduced into compositions of the present invention in amounts that allow delivery of an appropriate dosage of the agent to the damaged tendon and/or the site of tendon reattachment. In most cases, dosages are determined using guidelines known to practitioners and applicable to the particular agent in question. The amount of an additional biologically active agent to be included in a composition of the present invention can depend on such variables as the type and extent of the condition, the overall health status of the particular patient, the formulation of the biologically active agent, release kinetics, and the bioresorbability of the biocompatible matrix. Standard clinical trials may be used to optimize the dose and dosing frequency for any particular additional biologically active agent.

A composition for the treatment of tendons and/or bone, according to some embodiments, further comprises other bone grafting materials with PDGF including autologous bone marrow, autologous platelet extracts, allografts, synthetic bone matrix materials, xenografts, and derivatives thereof.

Methods of Treating and Reattaching Tendons

The present invention also provides methods for the attachment or reattachment of tendons to bone, the strengthening of tendon attachment to bone as well as the treatment of tendons, such as tendons exhibiting tearing, delamination, or any other strain or deformation. In one embodiment, a method for reattaching a tendon to bone comprises providing a composition comprising a PDGF solution disposed in a biocompatible matrix and applying the composition to at least one site of tendon reattachment on the bone. In another embodiment, a method of strengthening the attachment of a tendon to a bone comprises providing a composition comprising a PDGF solution disposed in a biocompatible matrix and applying the composition to at least one site of tendon attachment to bone. Methods of strengthening tendon attachment to bone, in some embodiments, assist in preventing or inhibiting tendon detachment from bone, such as in rotator cuff injuries.

The present invention also provides methods of treating rotator cuff tears. In one embodiment, a method for treating rotator cuff tears comprises providing a composition comprising a PDGF solution disposed in a biocompatible matrix and applying the composition to at least one site of tendon reattachment on the humeral head. In some embodiments, applying the composition to at least one site of tendon reattachment can comprise molding the composition to the contours of the reattachment site on the humeral head. A composition, for example, can be molded into a channel formed on a surface of the humeral head for receiving the detached tendon. The composition may be applied to the vicinity of the insertion site of the tendon into bone to further strengthen the attachment.

In some embodiments, a method for treating rotator cuff tears further comprises disposing at least one anchoring means, such as a bone anchor in the humeral head, wherein the bone anchor further comprises a PDGF composition, and coupling at least one detached tendon to the bone anchor. In embodiments of the present invention, tendons can be secured to bone anchors through sutures. Sutures may also be soaked in PDGF solutions or coated in PDGF compositions before use. Examples 2-4 describe three different methods for treating rotator cuff tears.

In another embodiment, a method of treating a tendon comprises providing a composition comprising a PDGF solution disposed in a biocompatible matrix and applying the composition to a surface of at least one tendon. In some embodiments, the at least one tendon is an injured or damaged tendon, such as tendon exhibiting tearing, delamination, or any other deformation.

PDGF solutions and biocompatible matrices suitable for use in compositions, according to embodiments of methods of the present invention, are consistent with those provided hereinabove.

Kits

In another aspect, the present invention provides a kit comprising a solution comprising PDGF in a first container and a second container comprising a biocompatible matrix. In some embodiments, the solution comprises a predetermined concentration of PDGF. The concentration of PDGF, in some embodiments, can be predetermined according to the nature of the tendon being treated. The kit may further comprise a scaffolding material and the scaffolding material may further comprise a biocompatible binder. Moreover, the amount of biocompatible matrix provided by a kit can be dependent on the nature of the tendon being treated. Biocompatible matrix that may be included in the kit may be a scaffolding material, a scaffolding material and a biocompatible binder, and/or bone allograft such as DFDBA or particulate DBM. In one embodiment the bone scaffolding material comprises a calcium phosphate, such as β-TCP. In

another embodiment, a scaffolding material comprises a type I collagen patch as described herein. A syringe, in some embodiments, can facilitate disposition of the PDGF solution in the biocompatible matrix for application at a surgical site, such as a site of tendon attachment to bone. The kit may also contain instructions for use.

The following examples will serve to further illustrate the present invention without, at the same time, however, constituting any limitation thereof. On the contrary, it is to be clearly understood that resort may be had to various embodiments, modifications and equivalents thereof which, after reading the description herein, may suggest themselves to those skilled in the art without departing from the spirit of the invention.

EXAMPLE 1

Preparation of a Composition Comprising a Solution of PDGF and a Biocompatible Matrix

A composition comprising a solution of PDGF and a biocompatible matrix was prepared according to the following procedure.

A pre-weighed block of biocompatible matrix comprising β-TCP and collagen was obtained. The β-TCP comprised pure β-TCP particles having sizes ranging from about 75 μm to about 300 μm. The β-TCP particles were formulated with approximately 20% weight percent soluble bovine collagen binder. A β-TCP/collagen biocompatible matrix can be commercially obtained from Kensey Nash (Exton, Pa.).

A solution comprising rhPDGF-BB was obtained. rhPDGF-BB is commercially available from Chiron Corporation at a stock concentration of 10 mg/ml (i.e., Lot # QA2217) in a sodium acetate buffer. The rhPDGF-BB is produced in a yeast expression system by Chiron Corporation and is derived from the same production facility as the rhPDGF-BB that is utilized in the products REGRANEX, (Johnson & Johnson) and GEM 21S (BioMimetic Therapeutics) which has been approved for human use by the United States Food and Drug Administration. This rhPDGF-BB is also approved for human use in the European Union and Canada. The rhPDGF-BB solution was diluted to 0.3 mg/ml in the acetate buffer. The rhPDGF-BB solution can be diluted to any desired concentration according to embodiments of the present invention.

A ratio of about 91 μl of rhPDGF-BB solution to about 100 mg dry weight of the β-TCP/collagen biocompatible matrix was used to produce the composition. The rhPDGF-BB solution was expelled on the biocompatible matrix with a syringe, and the resulting composition was blended and molded into a thin strand for insertion into a 1 cc tuberculin syringe for placement at a site of tendon reattachment.

EXAMPLE 2

Treating Rotator Cuff Tears with an Open Repair Method

Open repair is performed without arthroscopy, and is typically used for larger rotator cuff injuries. In accordance with this method of the present invention, a surgeon makes a two- to three-inch incision over the shoulder and separates the deltoid muscle from the anterior acromion to gain access to and improve visualization of the torn rotator cuff. The deltoid muscle should only be detached to the extent necessary to gain sufficient access to the rotator cuff injury. Following the rotator cuff repair procedure, the deltoid is repaired with sutures to close the longitudinal divisional of the muscle.

The surgeon then identifies the detached end of the involved tendon(s) (infraspinatus, supraspinatus, teres minor, and/or subscapularis) and the remaining tendon stump is cut away or removed from the humeral head preferably with a rasp, rongeur, scalpel or high speed bur and/or shaver. The surgeon may perform an acromioplasty (removal of bone spurs from the undersurface of the acromion) and remove any scar tissue that has built up on the tendon. Following debridement, cortical bone of the humeral head is abraded so as to produce bleeding bone and provide access for migrating mesenchymal stem cells of the bone marrow. In accordance with one embodiment of the method of the present invention, the cortical bone is removed so as to form a small channel in the humeral head that corresponds in shape and size to the original tendon attachment footprint. Preferably the channel is formed adjacent to the articular cartilage of the shoulder joint.

Prior to reattachment of the tendon, the surgeon may drill small holes within the channel through the bone. These holes may be used to affix bone anchors (preferably bone anchor screws). The bone anchors may be formed from any biocompatible material, and are preferably made of either a biocompatible metal or a resorbable composition. In accordance with an embodiment of the invention, bone anchor screws are affixed in a double row arrangement. The anchors thereby become an attachment point used to affix sutures to the humeral head.

A pilot hole is first drilled prior to insertion of the anchors. A PDGF composition in accordance with the present invention is then put into the pilot hole prior to insertion of the anchor. In one embodiment, injectable forms of the PDGF composition of the present invention are injected into the pilot holes.

As shown in FIG. **1**, in an alternative embodiment, a self-tapping self-drilling cannulated anchor **10** is used without the use of an initial pilot hole. Anchor **10** includes a needle access port **12** at or near its proximal end **14**, a central channel **16** extending along the axis of anchor **10**, and one or more exit ports, including radial exit ports **18** along the axis of anchor **10**, and/or a distal exit port **20** located near the distal end **22** of anchor **10**. In one embodiment, anchor **10** is drilled into the channel. Preferably a plurality of anchors **10** are used. Once inserted into the humeral head, a needle is inserted into the needle access port **12** of anchor **10**, and a PDGF composition of the present invention is injected into the central channel **16**. A sufficient amount of PDGF composition is injected into the anchor such that the PDGF composition fills the central channel **16** and flows out of the radial exit ports **18** and/or distal exit port **20** and into the surrounding bone. Any effective amount or concentration of PDGF composition may be used. In one embodiment, approximately 0.1 to 1.0 cc of a composition having approximately 0.3 to 1 mg/ml of PDGF is injected into each anchor or pilot hole.

In accordance with an embodiment of the present invention, the exit ports included in anchor **10** may be of varying diameter in order to regulate the rate at which the PDGF migrates into the surrounding bone. In addition, the rate of PDGF release within the surrounding bone is regulated by utilizing different PDGF formulations in the various anchors inserted into the channel. For example, the rate of PDGF release is prolonged by using more viscous compositions in certain anchors, or by using PDGF compositions comprising a matrix with extended PDGF release characteristics.

Alternatively, the drilled holes are used to affix sutures directly to the humeral head without the use of bone anchors.

In accordance with the next step of the method of the present invention, a PDGF composition is applied to substantially cover the channel. The PDGF composition used to cover the channel is in the form of either a solution, a putty, or gel, as described herein above. Alternatively, the PDGF composition is in the form of a pad. The pad may be composed of a substrate that is hydrated with a PDGF solution. The substrate is made from fibrous type I collagen, collagen hydrogel, crosslinked hyaluronic acid, porcine small intestine submucosa (SIS), polylactic acid/polyglycolic acid, or cellulose.

After the channel is covered with the PDGF composition, the proximal end of the tendon is then placed over the PDGF composition and into the channel. The tendon is secured in place by use of sutures that pass through tendon, the PDGF composition and into bone or through the eyelets of the bone anchors. Any of the various standard suturing techniques known to those skilled in the art (e.g., Mason Allen, mattress, simple suturing) may be used.

In accordance with an embodiment, the sutures are also impregnated with a PDGF solution prior to use. The sutures may be soaked in or saturated with a PDGF composition. Any effective amount or concentration of PDGF composition may be used. In one embodiment, PDGF at concentrations of 0.1, 0.3, or 1.0 mg/mL may be used to wet the suture prior to use. Furthermore, the suture may be treated with glycerol, gelatin, or paraffin wax to slow the release of PDGF in a manner that is consistent with the wound healing process.

The PDGF composition may be applied adjacent to and/or over the tendon to augment healing of the tendon/bone margins. This PDGF composition may be in the form of a solution, putty, gel, or pad, and may be secured in position with the same sutures used to secure the tendon.

Following the implantation of the PDGF composition and suturing of the rotator cuff, all dissected muscles are sutured closed, the overlying fascia is repaired, and lastly the patient's skin is closed with sutures or staples.

EXAMPLE 3

Treating Rotator Cuff Tears with a Mini-Open Repair Method

A mini-open rotator cuff repair procedure involves using both an arthroscopic technique for part of the process in conjunction with a limited open technique typically done through a 3 cm to 5 cm incision. This technique also incorporates an arthroscopy to visualize the tear, assess and treat damage to other structures within the joint (i.e., labrum and remove the spurs under the acromion). Arthroscopic removal of spurs (acromioplasty) avoids the need to detach the deltoid muscle. Thereafter, an arthroscopic decompression may be performed. The decompression may be followed by a release and mobilization of the tendons and placement of tagging sutures. These steps may be done arthroscopically or open. The final steps are done in an open procedure, but via the smaller opening. In particular, a small lateral deltoid split is performed in order to place tendon-gripping sutures on the previously mobilized cuff and to fix the cuff to bone using either suture anchors or transosseous sutures.

In accordance with one embodiment, a mini-open repair method of the present invention comprises the following steps.

The patient is prepared in accordance with standard techniques for patient positioning and marking. The arthroscope is placed in the glenohumeral joint through the posterior portal and a thorough evaluation of the joint is performed. The rotator cuff tear is identified and a lateral portal is created.

Rotator cuff mobilization starts with an intra-articular release. A hooked electrocautery device is used to release the cuff from the glenoid labrum. This allows mobilization of the entire cuff if necessary (anterior to posterior). Once the intra-articular release has been performed, the arthroscope is directed to the subacromial space.

An arthroscopic subacromial bursectomy is performed. The tuberosity (area of rotator cuff insertion) is decorticated. In some applications the tuberosity may be only slightly decorticate with no formal channel being created. A shaver is used to debride any of the torn cuff edge that appears to be nonviable or attenuated. Stay sutures are placed in the edge of the cuff tear approximately 1 cm apart. The stay sutures may be pretreated with a PDGF composition in the manner described above in Example 2. Additional releases of the cuff from the glenoid are performed as necessary.

The mini-open approach is then initiated with a horizontal lateral incision (3-4 cm long) being made over the lateral edge of the acromion. The deltoid muscle fibers are split to expose the rotator cuff tear.

If the tear is small and easily mobilized, sutures are placed through the edge of the cuff tear which is then repaired using suture anchors placed in the superolateral aspect of the greater tuberosity. For large tears under some tension, special intratendinous sutures are placed through the cuff and these are then repaired using the suture anchors placed in the superolateral greater tuberosity. Prior to securing the cuff, a PDGF composition is placed between the tendon and the humeral head in the same manner as described above regarding open procedures. In addition, the sutures used to secure the tendon may be pretreated with PDGF in a manner similar to that described above. The suture anchors may be of the type described above and illustrated in FIG. **1**. A PDGF composition may be injected into the suture anchors or into the suture anchor holes as described above. The surgery is completed in accordance with known closure techniques.

This arthroscopically assisted open repair has limitations when dealing with large or massive rotator cuff repairs. The necessary surgical releases can be difficult, if not impossible, to perform through a small trans-deltoid split. When compared to complete arthroscopic repair, the mini-open repair provides more secure bone-to-tendon fixation since tendon gripping sutures can be used.

EXAMPLE 4

Treating Rotator Cuff Tears with an All-Arthroscopic Repair Method

This technique uses multiple small incisions (portals) and arthroscopic technology to visualize and repair the rotator cuff. In addition, in accordance with the present invention this technique utilizes injectable or small encapsulated PDGF compositions that are capable of insertion through a keyhole incision or a cannula so that they are amenable to use with arthroscopic techniques.

In accordance with one embodiment, an arthroscopic repair method of the present invention comprises the following steps. The patient is prepared in accordance with standard techniques for patient positioning, assessment and

marking. One or two very small (1 cm) incisions, or "portals" are made, preferably one in the front and one behind the shoulder joint. Through these small portals, hollow instruments called cannulae are placed that irrigate the inside of the shoulder joint with sterile saline and inflate the joint with clear fluid. The cannulae allow the placement of an arthroscopic camera and specially designed instruments within the shoulder joint. The surgeon inserts a camera into the joint and maneuvers the camera around the joint in order to perform diagnostic arthroscopy.

In the most common cases the diagnostic arthroscopy reveals that the supraspinatus tendon is torn and/or pulled back slightly from its normal attachment at the greater tuberosity of the humerus. These smaller tears which are non-retracted or minimally-retracted only need to be freshened or debrided back to stable, healthy tendon tissue, then mobilized back to the tuberosity and fixed in place. The surgeon utilizes suture anchors to hold the tear in position while it heals. As with anchors used in the procedures described in Example 2, these anchors can be made of metal or absorbable compounds. In addition, the anchors are be screwed or pressed into the bone of the attachment site and the attached sutures used to tie the edge of the rotator cuff in place.

Prior to securing the tendon, a protected PDGF composition is placed between the tendon and the humeral head. The material may be placed in the bone anchor holes as well as across the decorticated surface of the humeral head. In the event that the humeral head is not prepared by decortication, the PDGF composition is placed against the cortical bone of the humeral head, and the tendon sutured into place in a standard manner. The sutures used to secure the tendon may be impregnated with PDGF in a manner similar to that described above. The suture anchors may be of the type described above and illustrated in FIG. **1**. An injectable PDGF composition may be injected into the suture anchors by inserting a needle through one of the cannula.

As tears become larger, they deform and the tendon tissue shrinks Thus, larger tears need to be refashioned, repaired side-to-side, or zipped closed using a technique called margin convergence. This technique is analogous to zippering shut an open tent flap. The rotator cuff tissue is freed from a scarred, retracted position. A protected PDGF composition is then inserted through one of the cannula or directly through an incision. The protected PDGF composition comprises a PDGF composition as described herein above encapsulated in or otherwise associated with a membrane designed to protect the PDGF composition from the arthroscopic fluid environment of the surgical site (FIG. **3**). The PDGF can be released at the treatment site using a variety of techniques to protect the protein during the initial placement to avoid rapid loss from the site due to the use of high volumes of fluids associated with the surgical procedure. In one embodiment, a membrane displays an intrinsic charge that promotes ionic interactions operable to release the PDGF in response to changing ionic conditions at the treatment or reattachment site. In another embodiment, a membrane forms a covalent interaction with the PDGF that is reversible via hydrolysis or enzymatic digestion to release the PDGF at the reattachment or treatment site. Membranes for protecting PDGF, in some embodiments, comprise collagen, polysaccharides, nucleic acids, carbohydrates, proteins, polypeptides, poly(α-hydroxy acids), poly(lactones), poly(amino acids), poly(anhydrides), poly(orthoesters), poly (anhydride-co-imides), poly(orthocarbonates), poly(α-hydroxy alkanoates), poly(dioxanones), poly(phosphoesters), polylactic acid, poly(L-lactide) (PLLA), poly(D,L-lactide) (PDLLA), polyglycolide (PGA), poly(lactide-co-glycolide (PLGA), poly(L-lactide-co-D, L-lactide), poly(D,L-lactide-co-trimethylene carbonate), polyglycolic acid, polyhydroxybutyrate (PHB), poly(ε-caprolactone), poly(δ-valerolactone), poly(γ-butyrolactone), poly(caprolactone), polyacrylic acid, polycarboxylic acid, poly(allylamine hydrochloride), poly(diallyldimethylammonium chloride), poly(ethyleneimine), polypropylene fumarate, polyvinyl alcohol, polyvinylpyrrolidone, polyethylene, polymethylmethacrylate, carbon fibers, poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidone), poly(ethyloxazoline), poly(ethylene oxide)-co-poly(propylene oxide) block copolymers, poly(ethylene terephthalate) polyamide, and copolymers and mixtures thereof. Additionally, the PDGF may be enclosed in ceramic materials such as tricalcium phosphate, hydroxyapatite, calcium sulphates, or variations thereof. In addition osmotic pumps may be used to provide protected release of the protein.

The protected PDGF composition is then placed over the tear and is sutured in place using the same sutures to do the side-to-side repair of the tear, and thereby restore the tissue over the top of the humeral head. A second protected PDGF composition is then inserted in the same manner as the first PDGF composition. The second protected PDGF composition is placed between the humeral head and the repaired cuff tissue. The repaired cuff tissue is then fixed to the site it originally tore away from preferably using suture anchors. The sutures are then sewn through the second protected PDGF composition and torn edge of the cuff to complete the repair.

At the conclusion of the procedure, any incisions are closed using absorbable or removable sutures. The patient's shoulder is placed into a postoperative sling to protect the shoulder during the early postoperative period.

Absorbable suture anchors or implants are gradually absorbed and the sutures attached are incorporated into the healing tissues. When metallic anchors are used (a matter of surgeon preference), these are buried in the bone, and do not affect the integrity of the bone or the shoulder joint.

EXAMPLE 5

Treatment of Rotator Cuff Injuries with β-TCP/PDGF Compositions

This study evaluated the efficacy of compositions comprising a rhPDGF-BB solution combined with a biocompatible matrix comprising β-tricalcium phosphate and type I collagen for the treatment and/or repair of rotator cuff injuries.

Study Design

Nine (9) adult female sheep were used in the present study. Six of the animals were administered a test composition comprising a 0.3 mg/ml rhPDGF-BB solution combined with a biocompatible matrix comprising β-tricalcium phosphate and type I collagen. As provided herein, 0.3 mg/ml rhPDGF-BB solutions was prepared by diluting stock rhPDGF-BB solutions with 20 mM sodium acetate buffer. The β-TCP was in particulate form, the particles having an average diameter ranging from about 75 μm to about 300 μm. Moreover, the type I collagen was present in an amount of about 20 weight percent of the biocompatible matrix. The remaining three animals were administered a control composition comprising a 20 mM solution of sodium acetate buffer combined with a biocompatible matrix comprising β-tricalcium phosphate and type I collagen.

As part of the study, the animals underwent a period (two weeks) of tendon detachment from the humerus, allowing degenerative changes to begin in the infraspinatus tendon. The degenerative changes were similar to those observed clinically in rotator cuff injuries. After two weeks, the animals underwent a tendon reattachment procedure in which the infraspinatus tendon was reattached to the humerus. As provided herein, six of the animals received the test composition at the site of tendon reattachment and the remaining three animals received the control composition at the site of tendon reattachment. All animals were allowed to heal for six weeks. At the six week point, all the animals were imaged with MRI. Subsequent to imaging, all the animals were humanely sacrificed and biomechnical analysis was performed on three of the animals receiving the test composition and three of the animals receiving the control composition.

Surgical Protocol

All animals were determined to be Q-fever negative prior to being placed in this study. Food was withheld from each animal 24 to 48 hours prior to the procedures and water was removed the morning of surgery. Each animal was given a general health evaluation (subject to visual observation for attitude, activity, and ease in respiration, freedom for diarrhea and nasal discharge) prior to being placed on the study. Respiratory infection, temperature elevations, observed depression, lameness or anatomical abnormality resulted in rejection of an individual animal from the surgical procedure. Each animal was weighed within 7 days prior to the procedure. Blood was collected for a CBC and Chemistry Profile within 7 days of surgery. Twelve animals were examined and all were found to be acceptable candidates for surgery.

Acepromazine maleate 0.075 mg/kg and Buprenorphine 0.005-0.01 mg/kg were administered im prior to anesthetic induction. An intravenous injection consisting of Diazepam 0.22 mg/kg and Ketamine 10 mg/kg was given for induction of general anesthesia. A cuffed endotracheal tube was placed and general anesthesia maintained with Isoflurane 0.5-5% delivered in oxygen through a rebreathing system. Each animal was placed on a ventilator to assist respiration. A catheter was placed in a peripheral ear vein of each animal. A stomach tube was placed if regurgitation occurred.

All surgical procedures were conducted utilizing routine aseptic techniques. Pre-operative preparation was conducted in the animal preparation room adjacent to the operating room. The appropriate shoulder and surrounding areas of each animal were prepared by clipping the area. Each animal was then moved to the operating room, and the area cleansed with chlorhexidine scrub alternating with 70% isopropyl alcohol three times and painted with iodine solution. Each animal was then draped for sterile surgery. Lactated Ringer's Solution (LRS) was intravenously infused at a rate of about 10-20 ml/kg/hr during surgery. Cefazolin 1-2 gram was intravenously administered prior to the initial incision, and 0.5 g Cefazolin was placed in the flush solution for each surgery.

A. Tendon Detachment Surgical Procedure

A 15 cm curved incision was made over the posterolateral aspect of the shoulder joint. The incision was deepened, and the acromial portion of the deltoid muscle identified. The muscle was elevated at its cranial edge to expose the tendinous insertion of the infraspinatus muscle and its insertion into the proximal part of the humerus bone. The infraspinatus tendon was detached sharply from its insertion on the proximal humerus. The tendon was then wrapped in a 5 cm×3 cm sheet of PRECLUDE® (W.L. Gore & Associates, Newark, Del.). This allowed diffusion of nutrients to the tendon but inhibits scarring of the tendon to the surrounding tissues. The incision was closed in standard fashion. A 10 cm diameter softball was affixed to the hoof of the limb associated with the operation to inhibit weight bearing for 7 weeks post-operation. Cefazolin lg was intravenously administered. A 100 μg fentanyl patch was placed on each animal.

B. Tendon Reattachment Surgical Procedure

Two weeks following initial surgery, each animal received a second procedure to repair the shoulder which underwent tendon detachment. The same surgical approach was used as in the first surgery.

In all animals, a moderate degree of tendon retraction was observed as well as adhesions to the tendon and muscle belly except for the region protected by PRECLUDE. These adhesions were dissected, freeing the muscle prior to reattachment in each animal. In preparation for insertion of bone anchors, the surface of the greater tuberosity was decorticated with a bone rongeur so as to create a bleeding bone surface and provide access to mesenchymal stem cell migration. At the same time, a 4 mm drill hole, approximately 10 mm deep was created within the decorticated area to provide a reservoir for test or control material. Two self-tapping suture anchors (15 mm in length by 5 mm wide) were then screwed into bone and on either side of the drill hole, and placed approximately 12 mm apart. Following insertion of the anchors, the tendon was unwrapped and mobilized by blunt dissection. The tendon was grasped with no. 2 ETHIBOND® (Johnson and Johnson) braided polyester suture in a modified Mason-Allen technique.

Prior to the reattachment surgery, stock PDGF-BB solutions (1.0 mg/mL, 5 mL total) (Lot # AAI-0022006-5A) were diluted 1:3 in 20 mM acetate buffer (pH 6.0) to a final concentration of about 0.3 mg/mL. The residual amounts of stock diluted PDGF-BB solutions were assayed by UV spectrophotometry to confirm the final solution concentration as provided in Table 1.

TABLE 1

Stock and diluted solutions of PDGF

	PDGF Tube	OD	Stock Tube	Final Concentration (Undiluted) (0.53 Extinction Coefficient)
Final PDGF-BB Sample Dilutions	A	0.125	BMIG9	0.235849057
	B	0.188	BMIG10	0.354716981
	C	0.207	BMIG11	0.390566038
	D	0.187	BMIG12	0.352830189
	E	0.173	BMIG13	0.326415094
	F	0.181	BMIG15	0.341509434
	G	0	Acetate Buffer	0
	H	0	Acetate Buffer	0
	I	0	Saline**	0
Stock PDGF-BB Solutions	BMIG9	0.57	N/A	1.075471698
	BMIG10	0.515	N/A	0.971698113
	BMIG11	0.478	N/A	0.901886792
	BMIG12	0.5	N/A	0.943396226
	BMIG13	0.523	N/A	0.986792453
	BMIG15	0.508	N/A	0.958490566

* Equation for determining protein concentration (OD * dilution factor)/0.53 = Final concentration (mg/mL)
**Saline was used to hydrate β-TCP/type I collagen matrix due to a shortage of acetate buffer

Each animal received approximately 1 cc of a β-TCP/type I collagen matrix hydrated with either a 20 mM sodium acetate buffer solution (pH 6.0) or a 0.3 mg/mL rhPDGF-BB

solution. For each animal, a fresh stock of acetate buffer or rhPDGF-BB stock solution was opened and diluted to produce the hydrating solution. Hydrating solutions A-I used in the preparation of compositions for the treatment of the nine animals in the study are provided in Table 1. Moreover, Table 2 provides the assignment of each of the hydrating solutions (A-I) to the animals in the study.

TABLE 2

Assignment schedule of control and test compositions

Animal	Hydrating Solution	Applied dose of Test or Control Composition
G2437	G	1 cc
G1636	A	1 cc
G1637	E	1 cc
G1627	F	1 cc
G2923	H	1.5 cc
G2054	I	1 cc
G2051	D	1 cc
G1647	C	1 cc
G2922	B	1 cc

Using aseptic technique, a 1 cc β-TCP/type I collagen brick was hydrated (1:3 ratio, β-TCP/type I collagen:PDGF solution) in a sterile dish with 3 cc of rhPDGF-BB solution or acetate buffer. In the case of hydrating solution "I", an insufficient volume of acetate buffer was available, and sterile saline was substituted for acetate buffer. The material was mixed with a sterile stainless spatula for approximately 1 minute until a homogenous consistency was achieved. The spatula was then used to load a 3 cc syringe barrel with as much of the test or control material as possible, the plunger inserted, and the graduated volume noted.

Approximately 1 cc of the test or control composition was applied across the bony tendon footprint and within the drill hole created between the anchors using a 3 cc syringe. Due to muscle and tendon wasting, and retraction, a modest amount of force was required to reapproximate the tendon anteriorly with its footprint. The tendon was then permanently tied to the anchor resting on bed of bleeding bone and test composition. For all animals, the process of suturing the tendon into place caused displacement of approximately 300 uL of the test or control composition into the space adjacent to the tendon. The wound was then closed in a standard fashion, and Cefazolin lg iv was administered along with a 100 ug fentanyl dermal patch placed on each animal.

C. Post-Operative Care

The animals were returned to the pre/post operating room where postoperative monitoring was continued. In this environment, the animals were monitored during anesthetic recovery for physiological disturbances including cardiovascular/respiratory depression, hypothermia, and excessive bleeding from the surgical site. Supplemental heat was provided as needed. The endotracheal and stomach tubes were removed after the animals regained the swallow reflex and was breathing on their own. Cefazolin 1 gram and Buprenorphine 0.005-0.01 mg/kg were administered im once postoperatively as the last treatment of the day. Additional analgesic was given as deemed necessary by a staff veterinarian. Long term postoperative monitoring included inspection of surgical sites and return to normal physiological function and attitude. Each animal received im injections of antibiotics once daily for 3 days (Naxcel). Each animal was monitored and scored for pain daily for at least 5 days. Pain evaluation was according to The Assessment of Pain in Sheep and Goats after Orthopedic Surgery. Body temperature, pulse, and respiration were recorded for each animal on days 1-3. General health assessments were conducted daily for at least 14 days. After that time, animal health was monitored and changes to health status were noted. The same pre and post operative procedures were followed for both of the surgeries. The softball/casts were changed once during the duration of the study at four weeks after the first surgery. Seven weeks after the initial surgery (five weeks after the second), the softball was removed from the operative limb and the animals were allowed full movement of the leg.

Magnetic Resonance Imaging

Prior to the terminal procedure, all animals were imaged with a GE Healthcare Signa Hdx 1.5T MR imaging system on the operated shoulder. In both axial and coronal orientations, the animals were scanned first using a T1 weighted protocol, and second a T2 fat-suppressed protocol. Table 3 provides the imaging orientation and protocol for each animal.

TABLE 3

Imaging orientation and protocol

Orientation	Protocol
T1 Axial	FSE-XL, 16 FoV, 3 mm slice thickness, 0.5 mm slice gap, 256 × 192 × Z512 matrix, 2 Nex, 8.8 TE, 600TR
STIR Axial	FSE-XL, 16 FoV, 3 mm slice thickness, 0.5 mm slice gap, 256 × 192 × Z512 matrix, 3 Nex, 60 TE, 4500 TR, 150 IR
T1 Coronal	FSE-XL, 16 FoV, 3 mm slice thickness, 0.5 mm slice gap, 256 × 192 × Z512 matrix, 2 Nex, 8.8 TE, 600TR
STIR Coronal	FSE-XL, 16 FoV, 3 mm slice thickness, 0.5 mm slice gap, 256 × 192 × Z512 matrix, 3 Nex, 60 TE, 4500 TR, 150 IR

As determined by independent analysis by two certified radiologists blinded to the treatment groups, animals treated with the test composition comprising a rhPDGF-BB solution combined with a β-TCP/type I collagen matrix demonstrated superior healing of the infraspinatus tendon in comparison to animals treated with the control composition.

Subsequent to imaging, all the animals were humanely euthanized by bolus injection of pentobarbital (Euthansol B) 100-200 mg/kg. Necropsy and tissue collection were conducted on each euthanized animal for biomechanical and histological analysis.

Biomechanical Testing

Following sacrifice, the treated and contralateral shoulders of all animals were dissected for biomechanical testing. All dissected shoulders were first wrapped in saline soaked gauze, placed in individual, uniquely identified plastic bags, and frozen to −80° C. until time for testing. During testing, the contralateral shoulders were used to normalize animal to animal variability. Testing was performed using a biomechanical testing apparatus model number 150 kN from Instron of Norwood, Mass., in which the free tendon was affixed with a cryo-clamp. The humeral head was affixed by means of an intramedullary bolt passed through the humeral head in a clevis device arrangement. The tendon and humerus were then distracted at a rate of 4 mm/second until complete separation of the tendon and humerus was achieved. The force was recorded at 0.02 second increments. Mode of failure was also recorded. Table 4 summarizes the results of the biomechanical testing for each animal in the study.

TABLE 4

Summary of biomechanical testing results

Specimen	Treatment	File Name	Max Load (N)	Mode of Failure	Mean Force to Failure (N)
Contralateral Control	G2051R	Pull01d	1313	Avulsion	1269
Contralateral Control	G1627R	Pull02	1108	Avulsion	
Contralateral Control	G2054r	Pull05a	694	Tendon Tear	
Contralateral Control	G1636L	Pull08	1503	Bone Fracture	
Contralateral Control	G2437L	Pull09	1069	Avulsion	
Contralateral Control	G2923R	Pull12	1929	Bone Fracture	
Matrix	G2054L	Pull04	367	Tendon Tear	543
Matrix	G2923L	Pull10	625	Tendon Tear	
Matrix	G2437R	Pull11	636	Tendon Tear	
PDGF	G1627L	Pull03	1179	Avulsion	994
PDGF	G1636R	Pull06	960	Avulsion	
PDGF	G2051L	Pull07	845	Avulsion	

By applying a t-test to the above data to compare control composition versus test composition treated shoulders, a statistically significant (p=0.028) increase in load to failure was observed among animals treated with test composition comprising rhPDGF-BB. Table 5 provides a summary of the statistical analysis.

TABLE 5

Summary of statistical analysis
Normality Test: Passed (P = 0.648)
Equal Variance Test: Passed (P = 0.837)

Group Name	N	Missing	Mean	Std. Dev.	SEM
Matrix	3	0	550.000	152.069	87.797
PDGF	3	0	994.000	169.237	97.709

Difference: −444.000
T = −3.380 with 4 degrees of freedom. (P = 0.028)

The increased load to failure in shoulders treated with the test composition indicated that the test composition comprising PDGF provided a stronger tendon reattachment to the bone in comparison to the control composition.

Additionally, all tendons treated with the test composition exhibited failure at the tendon insertion by avulsion on the bone, whereas tendons treated with the control compositions failed in the midsubstance of the tendon through tearing and delamination. This difference in mode of failure suggests that the application of rhPDGF-BB increases the tensile strength and maturity of the tendon, which does not occur in the control group, resulting in avulsion from the insertion site.

EXAMPLE 6

Treatment of Rotator Cuff Injuries with β-Tricalcium Phosphate/PDGF Compositions

This study evaluated the efficacy of a composition comprising a rhPDGF-BB solution combined with a biocompatible type I bovine collagen matrix for the treatment and/or repair of rotator cuff injuries.

Experimental Design

Sheep were selected as an appropriate animal model for the present study. The biomechanical forces measured in the rotator cuff of sheep approximate those which occur in the human shoulder. The animals and protocol used in this study are the current benchmark standard for evaluating rotator cuff repair.

A total of forty (40) animals were studied. All the animals were female and skeletally mature as determined by plain film radiography to ensure closure of the physis. The 40 animals were divided into 5 treatment groups as provided in Table 6 below. All animals were randomly assigned to the treatment groups.

TABLE 6

Summary of animal treatment groups

	Treatment Group	Animals (n)	rhPDGF-BB	Imaging	Endpoint
1	Suture	8	0	MRI	Biomechanics
2	Matrix + Buffer	8	0	MRI	Biomechanics
3	Matrix + Dose I	8	0.3 mg/mL	MRI	Biomechanics
4	Matrix + Dose II	8	1.0 mg/mL	MRI	Biomechanics
5	Matrix + Dose III	8	3.0 mg/mL	MRI	Biomechanics

Animals of all groups underwent two procedures. The first procedure was a resection of the infraspinatus muscle and cutting of the rotator cuff tendon. The second procedure occurred two weeks from the tendon detachment surgery to repair the tendon to bone at its insertion on the humerus. Reattachment of the rotator cuff tendon was administered with bone anchors as provided herein.

Group 1 received only bone anchors and suture for the reattachment of the tendon. In addition to bone anchors and suture, Group 2 received a type I collagen matrix hydrated with sodium acetate buffer (20 mM Na Acetate, pH 6.0), the hydrated collagen matrix positioned at the site of tendon reattachment. Moreover, in addition to bone anchors and suture, Groups 3, 4, and 5 received a type I collagen matrix hydrated with a rhPDGF-BB solution (0.3 mg/mL, 1.0 mg/mL, and 3.0 mg/mL, respectively), the hydrated collagen matrix positioned at the site of tendon reattachment. Collagen matrices hydrated and applied to animals in Groups 2-5 were obtained and are commercially available from Kensey Nash Corporation of Exton, Pa. under the tradename BIO-BLANKET®.

Surgical Protocol

All animals were determined to be Q-fever negative prior to being placed in this study. Food was withheld from each animal 24 to 48 hours prior to the procedures and water was removed the morning of surgery. Each animal was given a general health evaluation (subject to visual observation for attitude, activity, and ease in respiration, freedom for diarrhea and nasal discharge) prior to being placed on the study. Respiratory infection, temperature elevations, observed depression, lameness or anatomical abnormality resulted in

rejection of an individual animal from the surgical procedure. Each animal was weighed within 7 days prior to the procedure. Blood was collected for a CBC and Chemistry Profile within 7 days of surgery.

Acepromazine maleate 0.05 mg/kg and Buprenorphine 0.005-0.01 mg/kg were administered im prior to anesthetic induction. An intravenous injection consisting of Diazepam 0.22 mg/kg and Ketamine 10 mg/kg was given for induction of general anesthesia. A cuffed endotracheal tube was placed and general anesthesia maintained with Isoflurane 0.5-5% delivered in oxygen through a rebreathing system. Each animal was placed on a ventilator to assist respiration. A catheter was placed in a peripheral ear vein of each animal. A stomach tube was placed if regurgitation occurred.

All surgical procedures were conducted utilizing routine aseptic techniques. Pre-operative preparation was conducted in the animal preparation room adjacent to the operating room. The appropriate shoulder and surrounding areas of each animal were prepared by clipping the area. Each animal was then moved to the operating room, and the area cleansed with chlorhexidine scrub alternating with 70% isopropyl alcohol three times and painted with iodine solution. Each animal was then draped for sterile surgery. Lactated Ringer's Solution (LRS) was intravenously infused at a rate of approximately 10-20 ml/kg/hr during surgery. Cefazolin 1-2 g was intravenously administered prior to the initial incision and 0.5 g Cefazolin was placed in the flush solution for every surgery.

A. Tendon Detachment Surgical Procedure

A 15 cm curved incision was made over the posterolateral aspect of the shoulder joint. The incision was deepened, and the acromial portion of the deltoid muscle was identified. The muscle was elevated at its cranial edge to expose the tendinous insertion of the infraspinatus muscle and its insertion into the proximal part of the humerus bone. The infraspinatus tendon was detached sharply from its insertion on the proximal humerus. The tendon was then wrapped in a sheet of PRECLUDE®. This allowed diffusion of nutrients to the tendon but inhibited scarring of the tendon to the surrounding tissues. The incision was closed in standard fashion. A 10 cm diameter softball was affixed to the hoof of the limb associated with the operation to inhibit weight bearing for 7 weeks post-operation. Cefazolin lg was administered iv. A 100 μg fentanyl patch was placed on the animal.

B. Tendon Reattachment Surgical Procedure

Two weeks following the tendon detachment surgery the animals were shaved and prepped for surgery. General anesthesia was administered to each animal as provided hereinabove. The shoulder was approached as described previously. The surface of the tuberosity was roughened with a rongeur to create a bleeding bone surface prior to anchor insertion. Two metal suture anchors were used, typically 6 mm in length by 2-3 mm wide (commercially available from Smith and Nephew Endoscopy of Andover, Mass.). Each anchor was screwed in within the boundary of the footprint until flush with the humeral surface. The center of both anchors were placed approximately 1 cm apart. The tendon was unwrapped and mobilized by blunt dissection. For animals receiving a type I collagen patch hydrated with acetate buffer or a rhPDGF-BB solution, a No. 2 ETHIBOND® braided polyester suture (Johnson and Johnson) looped through the anchors was first passed through the collagen patch, passed through the tendon, tied with a modified Mason-Allen knot, and pulled over the tendon footprint. The tendon was permanently tied to the anchor and the wound is closed in a standard fashion. FIG. **4** illustrates positioning of the collagen patch at the site of tendon reattachment.

Prior to implantation and to facilitate handling and placement, each collagen patch was cut in half using a sterile ruler and scalpel to create two (2) 1 cm^2 collagen patches. Subsequent to cutting and prior to implantation, each 1 cm^2 collagen patch was hydrated by application of 150 μL of acetate buffer or rhPDGF-BB solution for 5 minutes until completely saturated. As provided herein, all animals that received the type I collagen patch have sutures from each anchor passed through each 1 cm^2 patch with a needle driver, and the patch pushed along the sutures until it is positioned over the decorticated footprint.

The tissue layers of each animal were subsequently closed, the edges of the skin incision re-apposed, sutured, and stapled. Each animal received a post-operative analgesic to minimize pain. The operated limb had a softball placed under the hoof during this post-operative period, which allowed limited movement for five weeks. Five (5) weeks following the reattachment procedure, all animals were imaged by MRI, and the scans are assessed by a radiologist. At the time of MRI, the softballs and casts were removed. The following week, six (6) weeks post-reattachment, all animals were humanely sacrificed, and the rotator cuff and attached infraspinatus tendon collected for biomechanical testing.

In Vivo Observations and Measurements

Clinical Observations

Animals were observed daily until the terminal procedure. During the first 14 days post-operatively, the animals were observed for general attitude, appetite, urine/fecal production, appearance of the surgical site and respirator stress. Temperature, pulse and heart rate were recorded for the first 3 days post-operatively. Pain was assessed for a minimum of 7 days post-operatively according to the Evaluation Form for the Assessment of Pain in Sheep and Goats. Antibiotics were administered to an animal if infection developed at the surgical site and was noted in the observations. Body weights were recorded prior to each surgical procedure and before the terminal procedure. Food consumption was qualitative. Animals were monitored daily and the degree of appetite is recorded.

MRI Imaging

MRI scans were taken of each animal at the direction of the study sponsor. Each animal was sedated and then placed in a lateral decubitus position with the operated shoulder down. Each animal was restrained to the table, monitored, and scanned for approximately 20 minutes. Table 7 provides MRI sequence protocols. After scanning, each animal was revived. Scans are forwarded to designated radiologists for a blind review.

TABLE 7

MRI sequence protocols			
	Sagittal PD		Sagittal T1
tr	1000	tr	500
te	10	te	10
etl	4	etl	2
rbw	31	rbw	25
fov	14	fov	14
slice thick	4	slice thick	4
slice gap	0	slice gap	0
mtrx	512 × 512	mtrx	512 × 512
nex	3	nex	2
pulse seq	fse	pulse seq	fse

TABLE 7-continued

MRI sequence protocols

Coronal PD Fat/Sat		Sagittal PD Fat/Sat	
tr	1450	tr	1350
te	11	te	11
etl	4	etl	4
rbw	31	rbw	31
fov	14	fov	14
slice thick	4	slice thick	4
slice gap	0	slice gap	0
mtrx	512 × 512	mtrx	512 × 512
nex	3	nex	3
pulse seq	fse	pulse seq	fse

Necropsy

Eight (8) weeks following the tendon detachment surgery all animals were humanely sacrificed for tissue collection. The humerus and approximately four (4) inches of the humeral shaft were collected along with the attached infraspinatus tendon and approximately two (2) inches of muscle distal to the myotendinous junction. All tissues were promptly wrapped in saline soaked gauze, double wrapped in labeled sealed plastic bags, and frozen to −20° C. until they were thawed for biomechanical testing.

Biomechanical Testing

Biomechanical testing was performed by the Rhode Island Hospital Orthopedic Foundation, Inc. During biomechanical testing, contralateral shoulders of the animals were used to normalize animal to animal variability. Testing was performed using an biomechanical testing apparatus model number 150 kN from Instron of Norwood, Mass., in which the free tendon was affixed with a cryo-clamp. The humeral head was affixed by means of an intramedullary bolt passed through the humeral head in a clevis device arrangement. The tendon and humerus were then distracted at a rate of 4 mm/second until complete separation of the tendon and humerus was achieved. The force was recorded at 0.02 second increments. Mode of failure was also recorded.

Shoulders treated with a type I collagen patch saturated with a rhPDGF-BB solution demonstrated an improvement in the ultimate force to tendon separation from the shoulder. Table 8 summarizes the force required to separate the reattached tendon from the shoulder as a percentage of the force required to separate the normal contralateral from its insertion into the humerus.

TABLE 8

Summary of Biomechanical Testing

Group	% of Normal
1 (Suture only)	59.6
3 (Matrix, 0.3 mg/ml PDGF)	79.8
4 (Matrix, 1.0 mg/ml PDGF)	75.3
5 (Matrix, 3.0 mg/ml PDGF)	73.5

As displayed in Table 8, force to tendon separation was higher for shoulders treated with a type I collagen patch saturated with a rhPDGF-BB solution indicating a stronger reattachment of the tendon to the bone in comparison with suture only.

All patents, publications and abstracts cited above are incorporated herein by reference in their entirety. It should be understood that the foregoing relates only to preferred embodiments of the present invention and that numerous modifications or alterations may be made therein without departing from the spirit and the scope of the present invention as defined in the following claims.

The invention claimed is:

1. A method for treating damaged or injured tissue comprising:

providing a composition consisting essentially of a scaffolding material having a solution consisting essentially of of platelet-derived growth factor_(PDGF) and a buffer disposed therein, the scaffolding material consisting essentially of i) collagen or ii) collagen and a biocompatible binder, the scaffolding material having a porosity of at least 25%, and the solution having a PDGF concentration ranging from about 0.05 to about 5.0 mg/mL, and

applying the composition to the damaged or injured tissue.

2. The method of claim **1**, further comprising debriding non-viable tissue prior to applying the composition to the damaged or injured tissue.

3. The method of claim **1**, wherein the total amount of PDGF applied to the tissue during a treatment period ranges from about 1 μg to about 50 mg.

4. The method of claim **1**, wherein the total amount of PDGF applied to the tissue during a treatment period ranges from about 10 μg to about 25 mg.

5. The method of claim **1**, wherein the total amount of PDGF applied to the tissue during a treatment period ranges from about 100 μg to about 10 mg.

6. The method of claim **1**, wherein the scaffolding material provides a framework for new tissue growth to occur.

7. The method of claim **1**, wherein the collagen is a collagen patch, pad, gel or paste.

8. The method of claim **1**, wherein the collagen is a collagen patch or pad.

9. The composition of claim **1**, wherein the collagen is a type I, type II or type III bovine collagen.

10. The method of claim **1**, wherein the collagen is soluble type I bovine collagen.

11. The method of claim **1**, wherein the collagen has a density ranging from about 0.75 g/cm3 to about 1.5 g/cm3.

12. The method of claim **1**, wherein the collagen has a wet tear strength ranging from about 0.75 pounds to about 5 pounds.

13. The method of claim **1**, wherein the collagen is capable of absorbing water in an amount ranging from about 1× to 15× the mass of the collagen.

14. The method of claim **1**, wherein the solution has a PDGF concentration ranging from about 0.1 to about 1.0 mg/mL.

15. The method of claim **1**, wherein the solution has a PDGF concentration ranging from about 0.2 to about 0.4 mg/mL.

16. The method of claim **1**, wherein the solution has a PDGF concentration of about 0.3 mg/mL.

17. The method of claim **1**, wherein the scaffolding material comprises pores having a size distribution between about 1 microns to about 1,000 microns.

18. The method of claim **1**, wherein the PDGF solution is disposed within the pores of the scaffolding material.

19. The method of claim **1**, wherein the biocompatible binder is selected from the group consisting of alginic acid, arabic gum, guar gum, xantham gum, gelatin, chitin, chitosan, chitosan acetate, chitosan lactate, chondroitin sulfate, N,O-carboxymethyl chitosan, α-cyclodextrin, β-cyclodextrin, Y-cyclodextrin, sodium dextran sulfate, fibrin glue, lecithin, phosphatidylcholine derivatives, glycerol, hyaluronic acid, sodium hyaluronate, methylcellulose, car-

boxymethylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, a glucosamine, a proteoglycan, a starch, lactic acid, a pluronic acid, sodium glycerophosphate, glycogen, a keratin, silk, and derivatives and mixtures thereof.

20. The method of claim **1**, wherein the PDGF is PDGF-BB.

21. The method of claim **1**, wherein the PDGF is recombinant human (rh) PDGF-BB.

22. The method of claim **1**, wherein the buffer is sodium acetate.

23. The method of claim **1**, wherein the PDGF comprises a combination of intact rhPDGF-B (1-109) and fragments thereof.

24. The method of claim **1**, wherein the PDGF comprises at least 65% of intact rhPDGF-B (1-109).

25. The method of claim **1**, wherein the damaged or injured tissue is a soft tissue.

26. The method of claim **1**, wherein the damaged or injured tissue is a wound.

27. A method for treating damaged or injured tissue comprising:

providing a composition consisting of a scaffolding material having a solution consisting of of recombinant human platelet-derived growth factor-BB (rhPDGF-BB) disposed therein, wherein the scaffolding material is a porous collagen patch or pad, the scaffolding having a porosity of at least 25%, and the solution has an rhPDGF-BB and a buffer concentration ranging from about 0.1 to about 1.0 mg/mL in a buffer, and

applying the composition to the damaged or injured tissue.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 10,456,450 B2
APPLICATION NO. : 16/007486
DATED : October 29, 2019
INVENTOR(S) : Charles E. Hart et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 32, Claim 1, Line 8, "of of platelet-derived growth factor" should read -- of platelet-derived growth factor --.

Column 32, Claim 19, Line 65, "Y-cyclodextrin" should read -- γ-cyclodextrin --.

Column 33, Claim 27, Line 24-26, "of of recombinant platelet-derived growth factor-BB (rhPDGF-BB) disposed therein" should read -- of recombinant platelet-derived growth factor-BB (rhPDGF-BB) and a buffer disposed therein --.

Column 33, Claim 27, Line 29, "an rhPDGF-BB and a buffer concentration" should read -- an rhPDGF-BB concentration --.

Signed and Sealed this
Tenth Day of March, 2020

Andrei Iancu
Director of the United States Patent and Trademark Office